The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper 51

By: Trial Section Merits Panel
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

QUIG WANG, MITCHELL H. FINER
and XIAO-CHI JIA

Junior Party,
Application 08/333,680

v.

IMRE KOVESDI, DOUGLAS E. BROUGH,
DUNCAN L. MCVEY, JOSEPH T. BRUDER
and ALENA LIZONOVA

Senior Party
Application 08/258,416

Patent Interference No. 104,825 (CAS)

MEMORANDUM OPINION and ORDER
(Decision on remaining preliminary and miscellaneous motions)

I. Introduction

This is a decision on the remaining preliminary and miscellaneous motions filed by parties Wang and Kovesdi in Interference 104,825 following oral arguments on

March 25, 2003. Steven B. Kelber, Esq., Linda Judge, Esq. and Sue Jensen, M.D., appeared for party Wang. John Kilyk, Jr., Esq. and Heather R. Kissling, Esq. appeared for party Kovesdi.

Interference 104,825 involves recombinant replication-defective[1] adenoviral vectors[2] wherein one or more essential functions[3] of at least[4] adenoviral early gene regions[5] E2 ("ΔE2") or E4 ("ΔE4") or both ("ΔE2,ΔE4") are nonfunctional and complementing cells[6] therefore.

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[1] A replication-defective/deficient viral vector is a viral vector that is unable to replicate due to deficiencies in gene functions essential for replication (i.e., generation of viral progeny) to occur. Such viral vectors are able to replicate in complementing cell lines that provide the missing gene functions in *trans* or with the aid of a helper virus. [Paper 34, "GLOSSARY OF AGREED UPON TERMS," hereinafter "Glossary," p. 8.]

[2] An adenoviral vector is an adenovirus that can carry a heterologous nucleic acid sequence (i.e., a transgene) into a suitable host cell. A transgene is a gene that is not normally present in a cell or viral vector, also called a heterologous or foreign gene. A gene is a physical and functional unit of heredity, which carries information from one generation to the next. In molecular terms, a gene is the entire DNA sequence necessary for the synthesis of a functional polypeptide or RNA molecule. In addition to coding regions, most genes also contain non-coding intervening sequences (introns) and transcription-control regions. [Glossary, pp. 1, 4 and 10.]

[3] An essential gene is gene that codes for a function necessary for cell or viral viability or normal growth. Adenoviral essential gene functions are encoded by, e.g., the adenoviral early regions (e.g., the E1, E2 and E4 regions), late regions (e.g., the L1-L5 regions), genes involved in viral packaging, and virus-associated RNAs (e.g., VA-RNA I and/or VA-RNA II). The E3 region is not required for adenoviral growth in culture.

[4] For simplicity, the expressions ΔE2, ΔE4 and ΔE2,ΔE4 as used herein are intended to encompass replication-defective adenoviruses and adenoviral vectors wherein the E3 region and/or essential functions of the E1 region are also nonfunctional, e.g., because a part or all of the region has been deleted.

[5] The early region is an area of the adenoviral genome that contains adenovirus genes expressed before the onset of viral DNA replication. The early region is divided into the E1A, E1B, E2A, E2B, E3 and E4 regions.

[6] A complementing cell is a cell that enables growth of viral vectors deficient in gene functions essential for growth by providing the missing gene function(s) in *trans*. The 293 cell line, for example, is a permanent cell line of primary human embryonal kidney (HEK) cells transformed by sheared human adenovirus type 5 (Ad 5) DNA that expresses the adenoviral E1A and E1B genes.

Wang has filed one miscellaneous and four preliminary motions. Kovesdi has filed one miscellaneous and three preliminary motions. Wang preliminary motion 1, seeking a judgment of no interference-in-fact, has been denied (Paper 31).

Wang preliminary motions 2 through 4 seek judgment that Kovesdi claims 20-21, 24-26, 36-87, and 89-95 are unpatentable under 35 U.S.C. § 112, first and second paragraphs, as not enabled, not described and indefinite, respectively. We grant Wang preliminary motion 2 and deny Wang preliminary motions 3 and 4. Piggy-backed upon Wang preliminary motions 2 through 4 is a "contingent" request for judgment of no interference-in-fact between Wang's involved claims and Kovesdi claim 19 if any of motions 2 through 4 is granted. Wang's "contingent" request is denied. Wang miscellaneous motion 1 seeks to add U.S. Patent 5,994,106 ("Kovesdi '106"), claiming "a replication-competent adenovirus-free stock of vectors" to the interference. We deny Wang miscellaneous motion 1.

Kovesdi preliminary motion 1 seeks judgment that Wang claims 52 and 54 are unpatentable under 35 U.S.C. § 112, first paragraph, as not described. Kovesdi preliminary motion 2 seeks to designate Kovesdi claims 39, 45, 48, 51 and 94 as <u>not</u> corresponding to Counts 4 and 6. Contingent on the grant of Kovesdi preliminary motion 2, Kovesdi preliminary motion 3 seeks to amend Kovesdi claim 19. We grant Kovesdi preliminary motion 1, deny Kovesdi preliminary motion 2 and dismiss Kovesdi preliminary motion 3. Kovesdi miscellaneous motion 1 seeks to suppress Wang Exhibit 2043. Kovesdi miscellaneous motion 1 is dismissed as moot.

II. Findings of fact (FF)

The following findings of fact are supported by a preponderance of the evidence.

1. The junior party is Quig Wang, Mitchell H. Finer and Xiao-Chi Jai (**Wang**).

2. Wang is involved in the interference on the basis of U.S. application 08/333,680 ("Wang '680," Ex 2001) , filed November 3, 1994.

3. Wang's real party-in-interest is Cell Genesys, Inc.

4. The senior party is Imre Kovesdi, Douglas E. Brough, Duncan L. McVey, Joseph T. Bruder and Alena Lizonova (**Kovesdi**).

5. Kovesdi is involved in the interference on the basis of U.S. application 08/258,416 ("Kovesdi '416," Ex 1001), filed June 10, 1994.

6. Kovesdi's real party-in-interest is GenVec, Inc.

7. The subject matter of the interference is defined by six (6) counts. Counts 1, 3 and 5 are directed to recombinant adenoviral vectors unable to replicate due to deficiencies in essential gene functions of the E2, E4 and both E2 and E4 regions, respectively. Counts 2, 4 and 6 are directed to corresponding complementing cell lines therefor.

8. Count 1 is defined by Wang claim 46, wherein the two gene regions are E1 and E2A, or Kovesdi claim 57 or Kovesdi claim 72 (Paper 1, p. 5).

9. Wang claim 46 reads:

> 46. A recombinant adenoviral vector, wherein said vector comprises at least a lethal deletion or mutation in two gene regions selected from the group consisting of E1, E2A and E4 early gene regions; and additionally comprises a transgene so that when rescued the resulting recombinant adenovirus requires for replication at most complementation of genes of the E1, E2A and E4 adenoviral early gene regions.

10. Kovesdi claim 57 depends from claim 41 which depends from claim 36.

11. Kovesdi claim 36 reads:

> 36. A cell line that complements *in trans* an adenoviral vector having an adenoviral genome, said genome being deficient in one or more essential gene functions of each of two or more adenoviral early gene regions selected from the group consisting of the E1, E2A, and E4 regions of said adenoviral genome, wherein nucleic acid sequences in said cell line encoding products complementing for said essential gene functions of said E2A and E4 regions of the adenoviral genome are operably linked to inducible promoters or repressible promoters, and wherein said cell line is derived from HEK 293 cells or A549 cells.

12. Kovesdi claim 41 reads:

> 41. The cell line of claim 36, wherein said vector is deficient in one or more essential gene functions of at least the E1 and E2A regions of the adenoviral genome.

13. Kovesdi claim 57 reads:

> 57. An adenoviral vector that requires, for replication, complementation *in trans* of one or more essential gene functions of at least the E1 and E2A regions of the adenoviral genome, which vector has been prepared using the cell line of claim 41.

14. Count 2 is defined by Wang claim 48, wherein the two gene regions are E1 and E2A, or Kovesdi claim 41 (Paper 1, p. 5).

15. Wang claim 48 reads:

> 48. A packaging cell line derived from a 293 cell that supplies the function of the E2A and E4 early regions wherein the nucleotide sequences encoding the E2A and the E4 early gene regions are operably linked to an inducible promoter and that supports the growth of a recombinant adenoviral comparing a transgene, wherein said vector comprises at least a lethal deletion or mutation in two gene regions selected from the group consisting of E1, E2A and E4 early gene regions; and so that when rescued the resulting recombinant adenovirus requires for replication complementation of genes of the E1, E2A and E4 early gene regions.

16. Kovesdi claim 41 depends from Kovesdi claim 36. Both Kovesdi claims 36 and 41 have been reproduced above (FF 11-12).

17. Count 3 is defined by Wang claim 37 or Kovesdi claim 53 or Kovesdi claim 70 (Paper 1, p. 5).

18. Wang claim 37 reads:

> 37. A replication-defective recombinant adenovirus, wherein the genome of said adenovirus contains at least two lethal deletions, two lethal mutations, or one lethal deletion and one lethal mutation in the E1 and E4 early gene regions, so that the recombinant adenovirus requires for replication at most complementation of genes of the E1, E2A and E4 adenoviral early gene regions, wherein said recombinant adenovirus genome additionally contains a transgene.

19. Kovesdi claim 53 depends on claim 37 which depends on claim 36. Kovesdi claim 36 has been reproduced above (FF 11).

20. Kovesdi claim 37 reads:

> 37. The cell line of claim 36, wherein said vector is deficient in one or more essential gene functions of at least the E1 and E4 regions of the adenoviral genome.

21. Kovesdi claim 53 reads:

> 53. An adenoviral vector that requires, for replication, complementation *in trans* of one or more essential gene functions of each of at least the E1 and E4 regions of the adenoviral genome, which vector has been prepared using the cell line of claim 37.

22. Kovesdi claim 70 depends on claim 68.

23. Kovesdi claim 68 reads:

> 68. An adenoviral vector that is deficient in one or more essential gene functions in each of two or more adenoviral early regions selected from the group consisting of the E1, E2A, and E4 regions of the adenoviral genome, wherein said vector comprises one or more functional early or late region genes.

24. Kovesdi claim 70 reads:

> 70. The adenoviral vector of claim 68, wherein said vector is deficient in one or more essential gene functions in at least the E1 and E4 regions of the adenoviral genome.

25. Count 4 is defined by Wang claim 39 or Kovesdi claim 38 (Paper 1, p. 5).

26. Wang claim 39 reads:

> 39. A packaging cell line derived from a 293 cell that supports the growth of a replication defective recombinant adenovirus that carries at least a lethal deletion in each of adenovirus E1 and E4 early gene regions, so that the recombinant adenovirus requires for replication complementation of genes of both the E1 and E4 adenoviral early gene regions, comprising a cell line that supplies the function of the E1 early gene region and the E4 early gene region wherein nucleotide sequences encoding the E4 early gene region is [sic] operably linked to an inducible promoter.

27. Kovesdi claim 38 depends on claim 37 which depends on claim 36. Kovesdi claims 36 and 37 have been reproduced above (FF 11 and 20).

28. Kovesdi claim 38 reads:

> 38. The cell line of claim 37, wherein said cell line comprises at least ORF6 of the E4 region of the adenoviral genome.

29. Count 5 is defined by Wang claim 46 or Kovesdi claim 59 (Paper 1, p. 6).

30. Wang claim 46 has been reproduced above (FF 9).

31. Kovesdi claim 59 depends on claim 43 which depends on claim 36. Kovesdi claim 36 has been reproduced above (FF 11).

32. Kovesdi claim 43 reads:

> 43. The cell line of claim 36, wherein said vector is deficient in one or more essential gene functions of at least the E2A and E4 regions of the adenoviral genome.

33. Kovesdi claim 59 reads:

> 59. An adenoviral vector that requires, for replication, complementation *in trans* of one or more essential gene functions of each of at least the E2A and E4 regions of the adenoviral genome, which vector has been prepared using the cell line of claim 43.

34. Count 6 is defined by Wang claim 48 or Kovesdi claim 43 (Paper 1, p. 6).

35. Wang claim 48 has been reproduced above (FF 15).

36. Kovesdi claim 43 has been reproduced above (FF 32).

37. The claims of the parties are:

Wang	37-48, 52, 54, 56-57
Kovesdi	19-26, 36-87, 89-95

38. The claims of the parties which correspond to Count 1 are:

Wang	46, 56
Kovesdi	20-21, 24-26, 52, 56-58, 68-69, 72-73, 78-79, 84-87

39. The claims of the parties which correspond to Count 2 are:

Wang	48
Kovesdi	19, 36, 41-42, 89-90, 95

40. The claims of the parties which correspond to Count 3 are:

Wang	37-38, 46-47, 52, 54, 56
Kovesdi	20-21, 24-26, 52-56, 68-71, 78-79, 82, 84-87

41. The claims of the parties which correspond to Count 4 are:

Wang	39-44, 57
Kovesdi	19, 36-40, 89-90, 92-95

42. The claims of the parties which correspond to Count 5 are:

Wang	37, 46, 54, 56
Kovesdi	20-21, 24-26, 52-87

43. The claims of the parties which correspond to Count 6 are:

Wang	48, 57
Kovesdi	19, 36-41, 43-51, 89-90, 92-95

44. The claims of the parties which do not correspond to any of Counts 1 through 6, and therefore are not involved in the interference, are:

Wang	45
Kovesdi	22-23, 91

Other findings of fact follow below.

III. Kovesdi preliminary motion 2

Kovesdi moves pursuant to 37 CFR § 1.633(c)(4) for judgment that Kovesdi claims 39, 45, 48, 51 and 94, currently designated as corresponding to Counts 4 and 6, do not correspond to any of Counts 1-6 (Paper 37). Wang does not oppose.

45. Kovesdi claims 39, 45, 48, 51 and 94 are drawn to complementing cell lines, derived from HEK 293 or A549 cells, for replication defective adenoviral vectors wherein one or more essential gene functions of each of two or more adenoviral early gene regions selected from the group consisting of E1, E2A and E4 are nonfunctional, *wherein said cell line comprises ORF6 and no other ORF of the E4 region of the adenoviral genome* (Kovesdi claims 39, 45, 48 and 51) or *wherein said cell line comprises at least ORF6 and no other ORF of the E4 region of the adenoviral genome* (Kovesdi claim 94).

A. Technical background

46. It was known by at least 1983 that 293 cells, a line of human embryonic kidney ("HEK") cells transformed by sheared adenoviral DNA, supported the growth of E1

deletion mutant adenoviruses (Ex 1007,[7] p. 5383, ¶ 1 and Ex 3004[8]).

47. It was also known by 1983 that the W162 cell line, which contains an intact adenoviral E4 region, supported the growth of an E4 deletion adenovirus mutant (Ex 1007).

48. There are seven known open reading frames in the E4 region, i.e., ORF1, ORF2, ORF3, ORF4, ORF3/4, ORF6 and ORF6/7 (Ex 3002,[9] Figure 1a and Ex 1003,[10] p. 631, c. 1, ¶ 2).

49. In 1987, Cutt,[11] whose study focused on the products encoded by E4 ORFs 6 and 7, reported that

> [t]he 6/7 fusion polypeptides may be functionally, as well as structurally, related to the ORF 6 34K protein. ... Deletion of E4 ORFs 1 through 4 has no effect on virus viability in lytic infection of HeLa cells .... Mutant *dl*355 (ORF 6 deletion) is moderately defective for lytic growth, and *dl*366 (deletion of all E4 ORFs) is severely defective for viral growth .... Since ORFs 1 through 4 are dispensible for virus growth, the differences in the severities of the *dl*355 and *dl*366 phenotypes may be due to the presence (*dl*355) or absence (*dl*366) of the ORF 6/7 fusion products within infected cells. We speculate that the ORF 6 34K and ORF 6/7 fusion products allow *dl*355 to grow significantly better than *dl*366 in lytic

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[7] David H. Weinberg and Gary Ketner, "A cell line that supports the growth of a defective early region 4 deletion mutant of human adenovirus type 2," Proceedings of the National Academy of Sciences: USA, Vol. 80, pp. 5383-5386 (September 1983) (Ex 1007).

[8] Graham et al., "Characteristics of Human Cell Line Transformed by DNA from Human Adenovirus Type 5," Journal of General Virology, Vol. 36, pp. 59-67 (1977) (Ex 1006).

[9] Gary Ketner, Eileen Bridge, Anders Virtajnen, Catherine Hemstrom and Ulf Pettersson (Ketner et al.), "Complementation of adenovirus E4 mutants by transient expression of E4 cDNA and deletion plasmids," Nucleic Acids Research, Vol. 17, No. 8, pp. 3037-3048 (1989) (Ex 1002).

[10] Eileen Bridge and Gary Ketner (Bridge I), "Redundant Control of Adenovirus Late Gene Expression of Early Region 4," Journal of Virology, Vol. 63, No. 2, pp. 631-638 (February 1989) (Ex 1003).

[11] Cutt et al. (Cutt), "Analysis of Adenovirus Early Region 4-Encoded Polypeptides Synthesized in Productively Infected Cells," Journal of Virology, Vol. 61, No. 2, pp. 543-552 (February 1987) (Ex 1022).

> infection. ... Thus, the essential E4 sequences required for virus viability in lytic infection may reside solely within the amino terminus of ORF6. ... [Ex 1022, ¶ bridging pp. 550-551.]

50. In 1989, Bridge I reported

> ...(i) that the products of ORF 6 and ORF 3 can individually provide an E4 function that results in nearly normal late protein synthesis, (ii) that the E4-related protein synthetic defect is observed independently of a defect in DNA accumulation, and (iii) that although optimal plaque formation on noncomplementing cell lines requires the ORF 6 product, the ORF 3 product suffices for plaquing at a slightly lower efficiency (Ex 1003, p. 631, c. 2, ¶ 1).

In other words, "either ORF 6 or ORF 3 can individually provide a function that permits plaque formation, although ORF 6 appears to be required for optimal plaquing ability"[12] (Ex 1003, p. 636, c. 2, ¶ 5).

51. Also in 1989, Ketner et al. (including the authors of Bridge I) reported that "[p]lasmids carrying ORFs 1, 2, 3/4, 4, and 6/7 in the absence of ORFs 3 and 6 are inactive in complementing E4 mutants" (Ex 1002, p. 3046, c. 1, ¶ 3).

52. In 1993, Bridge II reported that "E4 products are not absolutely required for viral DNA replication" (Ex 1030,[13] p. 794, c. 2, ¶ 2). According to Bridge II, "[t]he removal of all E4 products from an infected cell by mutation would result in unregulated DNA

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[12] The plaque method is used to detect and count viruses. A mixture of virus, host cell and agar is poured into a Petri plate containing a hardened layer of agar growth medium to form a top monolayer of host cells. Each virus infects a host cell, multiplies and releases several hundred new viruses. The newly produced viruses infect adjacent host cells and more viruses are produced. After several viral multiplication cycles, all the host cells in the area surrounding the original virus are destroyed or lysed. This produces a number of clearings or "plaques" on the surface of the agar against a "lawn" or turbid background of uninfected host cells. See MICROBIOLOGY: An Introduction, by Tortora et al., pp. 321-22 (The Benjamin/Cummings Publishing Company, Inc., Menlo Park, California) (1982) (copy attached).

[13] Eileen Bridge, Susan Medghalchi, Sukithida Ubol, Minsun Leesong, and Gary Ketner (Bridge II), "Adenovirus Early Region 4 and Viral DNA Synthesis," Virology, Vol. 193, pp. 794-801 (1993) (Ex 1030).

synthesis, which in HeLa cell monolayers happens to permit the accumulation of viral DNA in an amount only slightly different from that produced by normally regulated synthesis" (id., p. 799, c. 2, ¶ 2). Bridge II proposed that the ORF 4 product acts to down-regulate viral DNA synthesis, while the ORF 3 (3/4) and ORF 6 products act either to moderate the effect of the ORF 4 product or to stimulate DNA replication by another mechanism (id.).

Bridge II is not inconsistent with the opening paragraph in Bridge I, i.e.,

> The adenovirus infectious cycle includes two programs of gene expression, early and late, which are characterized by the expression of different sets of viral genes and are separated by the onset of DNA replication. Expression of early region genes is necessary for normal progression from the early to the late program. In particular, the analysis of two large deletion mutants of early region 4 (E4) ... has implicated E4 in many of the events that occur as the late program begins; the mutants have complex phenotypes that include defects in late protein synthesis, late mRNA accumulation, DNA accumulation, and shutoff of host cell protein synthesis. ... [Ex 1003, endnotes omitted.]

nor with the statement in Bridge I "that the effect on late protein synthesis of E4 mutations is not simply the result of a failure of cells infected by E4 mutants to accumulate normal amounts of viral DNA" (Ex 1003, p. 636, c. 1, ¶ 3).

Based on the foregoing, one of ordinary skill in the art would have had a reasonable basis for believing that E4 ORF 6, in the absence of other E4 ORFs, would have been sufficient to complement ΔE4 adenoviral mutants, although apparently the exact mechanism(s) by which complementation occurred was unknown.

B. Rule 637(4)(ii)

Rule 637(4)(ii) requires a movant seeking to designate an application or patent claim as not corresponding to a count to show that the claim does not define the same

patentable invention as any other claim whose designation in the notice declaring interference as corresponding to the count the party does not dispute.

Rule 601(n) states

> Invention "A" is the *same patentable invention* as an invention "B" when invention "A" is the same as (35 U.S.C. § 102) or is obvious (35 U.S.C. § 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A".

Here, Kovesdi contends that Kovesdi claims 39, 45, 48, 51 and 94 do not define the same patentable invention as claims designated as corresponding to Counts 4 and 6, i.e, Kovesdi claims 19,[14] 36-38, 40-41, 43-44, 46-47, 49-50, 89-90, 92-93 and 95; and, Wang claims 39-44, 48 and 57 (Paper 37, pp. 8-10).

C. The invention defined by Kovesdi claims 39, 45, 48, 51 and 94 is not anticipated by the other Kovesdi or Wang claims designated as corresponding to Counts 4 and 6.

None of Kovesdi claims 39, 45, 48, 51 and 94 are anticipated by the other claims designated as corresponding to Count 4 or 6 because none of these other claims include the limitation that the complementing cell line "comprise ORF6 and no other ORF of the E4 region of the adenoviral genome."

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[14] According to Kovesdi (Paper 37, p. 9, n.1),

> Kovesdi claim 19 is directed to a 293 cell line stably transfected with one or more plasmids that include pSMT/ORF-6 (SF 9). Kovesdi claim 19, therefore, includes the 293/ORF6 cell line as one embodiment, along with several other cell embodiments. As a result, Kovesdi claim 19 encompasses the separately patentable subject matter of Kovesdi claims 39, 45, 48, 51, and 94, as well as the other subject matter that corresponds to the existing Counts. By way of the concurrently filed KOVESDI PRELIMINARY MOTION NO. 3, party Kovesdi seeks to amend Kovesdi claim 19 to remove the aforementioned separately patentable subject matter from Kovesdi claim 19. The discussion in this KOVESDI PRELIMINARY MOTION NO. 2 treats Kovesdi claim 19 as if so amended.

D. Kovesdi claims 39, 45, 48, 51 and 94 are obvious over the Wang claims corresponding to Counts 4 and 6 in view of Cutt, Ketner et al., Bridge I and/or Bridge II

Kovesdi contends that

> at the time of the filings of the Wang and Kovesdi applications, one of ordinary skill in the art was not aware that the protein encoded by E4 ORF6 is the only E4 product necessary for growth of an adenoviral vector deleted of the entire E4 region in a non-E4 complementing cell line. Moreover, one of ordinary skill in the art was not aware that a cell line with ORF6 and no other ORF of the E4 region could propagate an adenoviral vector with deficiencies in replication-essential gene functions of the E4 region as well as either or both of the E1 region and the E2A region, let alone that such a cell line would be superior to cell lines with ORF6 and other ORFs of the E4 region. While it was known that the E4 region contained seven ORFs, it was not known with any reasonable degree of certainty at that time which of these E4 ORFs are required to support adenoviral growth in a complementary cell line, particularly in the context of propagating an adenoviral vector with deficiencies in replication-essential gene functions of the E4 region as well as either or both of the E1 region and the E2A region. [Paper 37, ¶ bridging pp. 13-14, citation to Kovesdi's statements of material facts omitted.]

However, it would have been prima facie obvious to modify the cell line of Wang claims 39-44, 48 and 57, which can contain E4 ORF6 as well as other ORFs of the E4 region in its genome, by substituting E4 ORF6 and no other E4 ORF into its genome because E4 ORF6 encodes the only E4 product necessary for growth of an adenoviral vector deleted of the entire E4 region as disclosed by Cutt (Ex 1022), Ketner et al. (Ex 1002), Bridge I (Ex 1003) and Bridge II (Ex 1030), and because such a modification would also be expected to avoid down-regulation of DNA viral synthesis by the product of the E4 ORF4 as suggested by Bridge I and II. See § III. A. above.

E. Kovesdi fails to establish unexpected results using 293/ORF6 cell lines

A conclusion of prima facie obviousness, of course, does not end a patentability analysis. As stated in In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), "[t]here is always a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious."

Here, Kovesdi argues that a cell line comprising E4 ORF6 and no other E4 ORF, e.g., the 293/ORF6 cell line described in Kovesdi '416 Example 8, is characterized by "significantly advantageous properties" (Paper 37, ¶ bridging pp. 14-15). To wit, "the 293/ORF6 cell line has a substantially reduced probability of producing an undesirable replication-competent adenoviral vector (RCA) through homologous recombination with shared sequences between the complementing cell and an adenoviral vector propagated in the complementing cell" (id., p. 15).

53. Kovesdi '416 Example 8 is said to describe the preparation of a 293/E4 cell line (i.e., 293 cells containing adenoviral region E4 in their genome) said to be capable of complementing adenoviral vectors defective in both E1 and E4 functions, such as Ad_{GV}CFTR.12 (Ex 1001, pp. 28-30).

54. Similarly, Kovesdi '416 Example 9 is said to describe the preparation of a 293/ORF6 cell line (i.e., 293 cells containing only ORF6 of the E4 region in their genome) said to be capable of complementing adenoviral vectors deficient in the E1 and E4 functions, such as Ad_{GV}CFTR.12 (Ex 1001, p. 30).

Kovesdi has not pointed us to, and we do not find, where Kovesdi '416 describes

any comparative data between the 293/E4 and 293/ORF6 cell lines.

Although Kovesdi '416 identifies recombination events resulting in creation of RCA as a problem when using singly deficient adenoviral vectors in gene therapy (Ex 1001, ¶ bridging pp. 9-10), Kovesdi has not pointed us to, and we do not find, where Kovesdi '416 describes any scientific data relating to the incidence of recombination events resulting in RCA when using multiply deficient adenoviral vectors.

55. Dr. Brough, one of the Kovesdi inventors, testified that the 293/E4 and 293/ORF6 cell lines described in Examples 8 and 9 of Kovesdi '416 were subjected to standard virology analysis as described in his laboratory notebook (Exs 1032-1034) and in published work from his laboratory (Ex 1009) (Ex 1016, ¶¶ 6 and 7).

56. Dr. Ornelles testified for Kovesdi that he understood "that the 293/ORF6 cell lines described in Examples 8 and 9 of Kovesdi '416 were subjected to standard virology analysis as described in EXHIBITS 1009 and 1032-1034" (Ex 1018, ¶ 16).

57. Both declarants identified Exs 1001, 1009 and 1032-1034 as

Exhibit 1001 - U.S. Patent Application 08/258,416 ("the Kovesdi '416 application")

Exhibit 1009 - Brough et al., *J. Virol.* 70(9), 6497-6501 (1996)

Exhibit 1032 - Laboratory Notebook No. 6 of Douglas E. Brough, Ph.D., pp. 39-40

Exhibit 1033 - Laboratory Notebook No. 6 of Douglas E. Brough, Ph.D., p. 116

Exhibit 1034 - Laboratory Notebook No. 6 of Douglas E. Brough, Ph.D., pp. 140-141

(Ex 1016, ¶¶ 2 and 7; Ex 1018, ¶ 2).

58. Drs. Brough and Ornelles both testified that "in combining the feature of complementing for an E1-deficiency with the feature of complementing for an E4

deficiency, the 293/E4 cell line does not complement for either an E1-deficiency or an E4-deficiency as well as the 293 cell line or the W162 cell line, respectively, as measured by virus production levels (EXHIBIT 1033, page 116; EXHIBIT 1032, page 40)" (Ex 1016, ¶ 8; Ex 1018, ¶ 17).

Section 43 of the STANDING ORDER[15] states, in relevant part,

> In the event a party relies on a scientific test or data generated from a scientific test, the party relying on the test or data shall explain:
> (a) the reason why the test is being used and why the data is being relied upon;
> (b) how the test is performed;
> (c) how the data is generated using the test;
> (d) how the data is used to determine a value;
> (e) the acknowledged accuracy of the test; and
> (f) any other information which would aid the board in understanding the significance of the test or data.
>
> Any explanation should take place through affidavit testimony of a witness, preferably accompanied by citation to relevant pages of standard texts (which should be exhibits in the interference).

Neither Dr. Brough nor Dr. Ornelles has explained the data in Exs 1032 and 1033 in compliance with § 42 of the STANDING ORDER. Moreover, several of the handwritten entries in Exs 1032 and 1033 are illegible, while several of the legible entries raise questions about the accuracy and reliability of the data.

For example, Exhibit 1032 appears to contain a notation that the number of cells per dish was not accurately controlled and, therefore, the pfu/cell could not be reported reliably (p. 40, ll. 4-7). If the data is not statistically accurate, it is unclear how results could be credibly compared. Exhibit 1032, p. 40 also appears to reference some sort

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[15] Compare with ¶ 14.10 of the May 2003 revised STANDING ORDER (copy attached).

of "lag in virus production" (fourth line from bottom). This raises questions as to timing. Exhibit 1030 reported that "at higher multiplicities (25 to 50 plaque-forming units per cell) and late times after infection (24 hr), most E4 mutants accumulate viral DNA in amounts comparable to those found in cells infected by wild-type virus" (Ex 1030, p. 794, c. 2, ¶ 2). Since dl366 is an E4 mutant, it may be that either multiplicity of infection or time after infection is affecting the data in Exhibit 1032. Moreover, Exhibit 1032, p. 40 ends with the word "retest."

Furthermore, Exhibit 1032 appears to describe growing an E4-deficient adenoviral vector (dl366) in three different cell lines, i.e., an E4-complementing cell line (W162), an E1-complementing cell line (293) and an E1/E4-complementing cell line (clone #25).[16] ΔE4 vector dl366 not only grew in cell lines W162 and clone #25 (which would have been expected to supply dl366's missing E4 function), but also in the 293 cell line. It is unclear how an E1-complementing cell line would supply a missing E4 gene function.

Moreover, zinc chloride ($ZnCl_2$) was added in amounts of 0, 10 and 100 μM. It is unclear how added $ZnCl_2$ affects the data. Finally, it is unclear whether the results of "clone #25" are representative of the "293/E4" genus of complementing cell lines.

Therefore, Exhibit 1032 appears of little probative value.

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[16] Drs. Brough and Ornelles identified the materials used as "the 293 cell line (an E1-complementing cell line), the W162 cell line (an E4-complementing cell line), the 293/E4 cell line (an E1/E4-complementing cell line), the 293/ORF6 cell line (an E1/E4 complementing cell line), dl366 (an E4-deficient adenoviral vector), dl312 (an E1-deficient adenoviral vector), AdGVCFTR.10 (an E1-deficient adenoviral vector), AdRSVßgal.11 (an E1/E4-deficient adenoviral vector), and AdCFTR.11A (an E1/E4-deficient adenoviral vector)" (Ex 1016, ¶ 7; Ex 1018, ¶ 16).

The data in Exhibit 1033 is similarly unexplained. Further, there is the question of the presence (and amount) of $ZnCl_2$ again. Moreover, it appears that ΔE4 dl366 failed to grow in any of four 293/E4 complementing cell lines (#12, #23, #25 and #55). Yet, according to Exhibit 1032, dl366 grew in 293/E4 cell line #25.

Therefore, Exhibit 1033 also appears of little probative value.

59. Drs. Brough and Ornelles both further testified that "[d]espite the fact that the 293/ORF6 cell line comprises only a small portion of the E4 region ... the 293/ORF6 cell line nevertheless can propagate E1/E4-deficient adenoviral vectors (EXHIBIT 1009, page 6497, column 2, first complete paragraph)" (Ex 1016, ¶ 9 and Ex 1018, ¶ 18).

However, as discussed in § A above, one of ordinary skill in the art would have had a reasonable basis for believing that E4 ORF6, in the absence of other E4 ORFs, would have been sufficient to complement E4 adenoviral mutants. Indeed, Exhibit 1009 itself states, "[o]f the possible open reading frame (ORF) products encoded by the E4 region, only one, either ORF3 or ORF6, is absolutely required for viral growth in tissue culture (2, 10, 13, 18)" (Ex 1009, p. 6497, c. 1, last sentence of ¶ 2). Of the four references cited to support this statement, two, i.e., 2 and 18, are the Bridge I (Ex 1003) and Ketner (Ex 1002) 1989 articles discussed above. Therefore, the ability of E4 OFR6 to provide the necessary replication function of the entire E4 gene region is not inconsistent with the state of the art.

60. Drs. Brough and Ornelles still further both testified that "[s]trikingly [Dr. Brough]/surprisingly [Dr. Ornelles], and in contrast to the 293/E4 cell line described above, the 293/ORF6 cell line functions substantially as well as the 293 cell line in

propagating E1-deficient adenoviral vectors, and it functions substantially as well as the W162 cell line in propagating E4-deficient adenoviral vectors, as measured by virus production levels (EXHIBIT 1034, page 141)" (Ex 1016, ¶ 9 and Ex 1018, ¶ 18).

The data in Ex 1034 is unexplained. For example, the graph depicted on page 141 appears to involve testing six different cell lines:

(1) the E4-complementing W162 cell line,
(2) the E1-complementing 293 cell line,
(3) a #216- clone of a 293/ORF6 E1/E4 complementing cell line in the absence of an unknown,
(4) a #216+ clone of a 293/ORF6 E1/E4 complementing cell line in the presence of an unknown,
(5) a #406- clone of a 293/ORF6 E1/E4 complementing cell line in the absence of an unknown, and
(6) a #406+ clone of a 293/ORF6 E1/E4 complementing cell line in the presence of an unknown.

The presence of the unknown appears to have affected the virus production of the #216 clone by about a factor of ten, but not to have affected the virus production of the #406 clone. Parameters such as multiplicity of infection, test time after infection, etc. are undefined.

Moreover, the relationship between the numerical data on p. 140 (Ex 1034) and the graph on p. 141 (Ex 1034) is unstated. Assuming arguendo that the #xxx designations referred to clones of 293/ORF6 cell lines, then the data on p. 140 might be grouped as follows:

	dl312 (E1-deficient vector)	AdGVCFTR.10 (E1-deficient vector)	dl366 (E4-deficient vector)
293 (E1+ cell)	1300.000	565.000	0.875
W162 (E4+ cell)	238.000	0.010	2275.000
#112 (E1+, E4+ cell)	550.000	90.000	1.000
#118 (E1+, E4+ cell)	1700.000	240.000	14.000
#120 (E1+, E4+ cell)	850.000	270.000	1.000
#202 (E1+, E4+ cell)	3150.000	650.000	1.000
#209 (E1+, E4+ cell)	850.000	900.000	1.000
#216 (E1+, E4+ cell)	900.000	200.000	50.000
#304 (E1+, E4+ cell)	1450.000	210.000	-9.250
#406 (E1+, E4+ cell)	950.000	290.000	292.000
#408 (E1+, E4+ cell)	1090.000	850.000	1.000

We will not guess what significance this data compilation may or may not have. Therefore, Exhibit 1034 appears to be of little probative value.

61. Drs. Brough and Ornelles yet still further both testified that "the 293/ORF6 cell line surprisingly is much more efficient than the 293/E4 cell line in propagating E1/E4-deficient adenoviral vectors" (Ex 1016, ¶ 9 and Ex 1018, ¶ 18).

Neither declarant points to any evidence of record to support this conclusion. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight. See Rohm and Hass Co. v. Brotech Corp., 127 F.3d 1089, 1092, 44 USPQ2d 1459, 1462 (Fed. Cir. 1997) (nothing in the Federal Rules of Evidence or Federal Circuit jurisprudence requires the fact finder to credit the unsupported assertions of an expert witness).

62. Drs. Brough and Ornelles both declared that

> The 293/ORF6 cell line has other important advantages over the

> 293/E4 cell line. The ability to complement for deficiencies in replication-essential gene functions in an adenoviral vector with a cell line comprising ORF6 and no other ORF of the E4 region, as exemplified by the 293/ORF6 cell line, greatly reduces the amount of viral products expressed by the cell line and reduces the probability of producing an undesired replication-competent adenoviral vector (RCA) through homologous recombination with shared sequences between the complementing cell and an adenoviral vector propagated in the complementing cell. Stocks of adenoviral vectors free from contaminating virus, such as RCA, are desired for controlled gene transfer to patients. [Ex 1016, ¶ 10 and Ex 1018, ¶ 19.]

First, if less than all of the E4 ORFs are introduced into the genome of a complementing cell, then it appears logical that the complementing cell line will produce fewer viral products, i.e., the products encoded by the missing E4 ORFs will not be produced. Second, production of undesired RCA as argued above is not solely dependent upon the complementing cell line. As stated in the Brough et al. article, published more than two years after the June 10, 1994 filing date of Kovesdi '416, "Since no overlapping sequences between the new cell lines and the genome of the vector with E4 deleted exist, no generation of replication-competent virus by homologous recombination will occur" (Ex 1009, p. 6497, c. 2, ¶ 2). Nor have the parties pointed us to any evidence supporting a conclusion that any E4-deficient adenoviral vector can be propagated in a 293/ORF6 complementing cell line without generation of RCA. Thus, it appears to be a selected combination of complementing cell line and deletion adenoviral vector that is needed to avoid generation of RCA by homologous recombination.

Therefore, this argument, too, is insufficient to establish unexpected results of the 293/ORF6 cell line per se.

For the above reasons, Kovesdi preliminary motion 2 is **denied.**

IV. Kovesdi preliminary motion 3

Kovesdi moves pursuant to 37 CFR § 1.633(c)(2) to amend Kovesdi claim 19 to delete one embodiment, i.e., a 293 cell line that is stably transfected with a pSMT/ORF-6 plasmid, contending that this is a separately patentable invention from the subject matter of Counts 4 and 6 (Paper 38).

Kovesdi preliminary motion 3 is contingent upon the grant of Kovesdi preliminary motion 2. In view of our denial of Kovesdi preliminary motion 2, Kovesdi preliminary motion 3 is **dismissed** as moot.

V. Kovesdi preliminary motion 1

Kovesdi seeks judgment pursuant to 37 CFR § 1.633(a) that Wang claims 52 and 54 are unpatentable under 35 U.S.C. § 112, first paragraph (written description), contending that Wang '680 does not suggest an adenoviral vector comprising a lethal deletion or mutation in E4 "in which the region of the E4 early gene region which is deleted or mutated is open reading frame 6" (Paper 36). Wang opposes (Paper 50); Kovesdi replies (Paper 67).

To satisfy the written description requirement of the first paragraph of § 112, the specification must convey to one of skill in the art that the inventors had possession of the claimed subject matter at the time of filing. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). "One shows that one is 'in possession' of the invention by describing the invention, with all its claimed limitations." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966

(Fed. Cir. 1997).

A. Wang claims 52 and 54 specify that the claimed adenoviral vector has a deletion of *only* E4 ORF6.

63. Wang claim 52 depends on claim 38.

64. Wang claim 38 reads:

> 38. A replication-defective recombinant adenovirus, wherein the genome of said adenovirus contains at least two lethal deletions, two lethal mutations, or one lethal deletion and one lethal mutation in the E1 and E4 early gene regions, wherein an essential region of the E4 early gene region is deleted or mutated, so that the recombinant adenovirus requires for replication at most complementation of genes of both the E1 and E4 adenoviral early gene regions, and wherein said recombinant adenovirus genome additionally contains a transgene.

65. Wang claim 52 reads:

> 52. The replication-defective recombinant adenovirus of Claim 38 in which the region of the E4 early gene region which is deleted or mutated is open reading frame 6.

66. Wang claim 54 depends on claim 46.

67. Wang claim 46 reads:

> 46. A recombinant adenoviral vector, wherein said vector comprises at least a lethal deletion or mutation in two gene regions selected from the group consisting of E1, E2A and E4 early gene regions; and additionally comprises a transgene so that when rescued the resulting recombinant adenovirus requires for replication at most complementation of genes of the E1, E2A and E4 adenoviral early gene regions.

68. Wang claim 54 reads:

> 54. The recombinant adenoviral vector of Claim 46 in which the region of the E4 early gene region which is deleted or mutated is open reading frame 6.

In its opposition (Paper 50, pp. 4-5), Wang argues that its claims 52 and 54 should be interpreted as encompassing an adenoviral vector in which the region of the

E4 early gene region which is deleted or mutated is at least ORF6.[17] Wang's interpretation invites us to read the second "is" in claims 52 and 54 to "is at least." We decline to do so. Claims are interpreted as broadly as their terms reasonably allow consistent with the specification as it would be interpreted by one of ordinary skill in the art. In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997).

B. There is no original "ipsissimus verbis" disclosure of an adenoviral vector having a deletion of only E4 ORF6 in Wang '680.

69. There is no dispute that

(a) Wang claims 52 and 54 were added to Wang '680 by amendment (Ex 1037).

(b) Wang cited the working examples of Wang '680, specifically page 27, line 19 to page 28, line 13 and page 28, line 16 to page 30; line 1, as support for added claims 52 and 54 (Ex 1037, p. 6, ¶ 2).

(c) These cites do not refer to deletions or mutation of E4 ORFs except by reference to a specific E4-deletion mutant H5dl1014 for construction of recombinant E4-deficient viruses.

(d) E4-deletion mutant H5dl1014 contains two deletions, one from map units 92 to 93.8 and the other from map units 96.4 to 98.4 (Ex 1031, p. 31, ll. 31-32), which destroy all of the E4 ORFs, except E4 ORF4 (id., p. 31, l. 33 - p. 32, l. 1).

[See Paper 50, p. 1 where Wang admits Kovesdi facts 9-12 as set forth in Paper 36.]

Thus, there is no original ipsissimus verbis disclosure of a recombinant

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[17] Wang independent claims 38 and 46 are broadly interpreted as encompassing adenoviral vectors having a deletion of at least E4 ORF6 in view of their recitation both of containing "at least" a lethal deletion and/or mutation in E4 and of requiring "at most" complementation of genes of E4 (allowing for complementation of all E4 genes).

adenoviral vector "in which the region of the E4 early gene region which is deleted or mutated is open reading frame 6," as recited in Wang claims 52 and 54.

However, ipsissimus verbis disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to the skilled artisan that the inventor had possession of the subject matter in question. In re Edwards, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978).

C. Wang '680 neither specifically identifies nor suggests E4 ORF6 as a region of E4 to delete or mutate. Therefore, Wang '680 does not reasonably convey to one skilled in the art that Wang was in possession of an adenoviral vector "in which the region of the E4 early gene region which is deleted or mutated is open reading frame 6," as recited in Wang claims 52 and 54.

70. Wang '680 describes

(a) an aspect of Wang's invention as "the successful establishment of a novel packaging cell line which supports the growth of both the E1 and E4 deletions in E1 and E4 deficient adenoviruses" (Ex 1031, p. 10, ll. 8-12).

(b) overexpression of the E4 gene region would be expected to result in the death of a host cell because the product of the E4 ORF6 in association with the product of the E1B gene inhibits cellular mRNA transport and thereby cellular protein synthesis in the host cell (id., p. 10, ll. 12-18).

(c) trans-activation of the E1A gene product in the parental 293 cells as causing the overexpression of the E4 genes (id., p. 10, ll. 18-23).

(d) replacing the E4 promoter[18] with an inducible promoter[19] to solve this problem

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[18] A promoter is a nucleotide sequence that can bind RNA polymerase, resulting in the initiation of transcription. The promoter is essential for the initiation of transcription of RNA from DNA and, therefore,

(id., p. 10, ll. 23-26), e.g., by uncoupling E1A trans-activation from induction of the E4 gene (id., p. 10, l. 26 - p. 11, l. 25).

Wang argues that in order to be worried about complementing E4 ORF6, Wang had to recognize the importance of deleting ORF6 selectively from the various E4 ORFs and had to be in possession of an E4 ORF6 deleted adenoviral vector (Paper 50, p. 6).

It appears to us that Wang was in possession of complementing (host) cell derived from 293 parent cells transformed by introduction of a full length E4 sequence under the control of an inducible promoter (see e.g., Ex 1031, p. 11, ll. 22-26). Wang '680 describes this complementing cell line, 293-E4, as capable of supporting the growth of adenoviruses containing deletions in E1, E3 and E4 (id., p. 11, ll. 26-30). Wang '680 describes complementing the entire E4 gene region, not just E4 ORF6, in the passage discussed above. Wang '680 suggests controlling the expression of all the E4 genes, not just E4 ORF6 (although it may have been obvious-to-try to focus on controlling expression of E4 ORF6). However, a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of the invention. Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

Wang further argues that

> ...[Wang '680] specifies, page 9, line 5, that a major feature of the application is the introduction of "a second essential gene region deletion into the adenoviral vector." E4 is specifically identified as a target gene region. Even Kovesdi's own involved '416 application specifically acknowledges that one of skill in the art, taught to delete an essential

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is essential for gene expression. [Glossary, p. 7.]

[19] An inducible promoter is a promoter whose activity is upregulated in the presence of an inducer molecule (Glossary, p. 5).

gene region of E4, would specifically and selectively delete ORF6. Kovesdi's own patent application characterizes ORF6 as "the only absolutely essential E4 product necessary for virus growth in a non-E4 complementing cell line." [Paper 50, ¶ bridging pp. 6-7.]

However, as pointed out by Kovesdi in its reply (Paper 67, p. 8), it is Kovesdi '416 itself that teaches "ORF6 is the only absolutely essential E4 product necessary for virus growth in a non-E4 complementing cell line" (Ex 1001, p. 28, ll. 10-12). Moreover, "... one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say 'here is my invention.' In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure" (In re Ruschig, 379 F.2d 990, 994-95, 154 USPQ 118, 122 (CCPA 1967). Here, Wang '680 discloses deletion of the E4 region without any "blaze marks" leading the skilled artisan to deletion of E4 ORF6 specifically.

D. Wang's reliance on documents incorporated by reference in Wang '680 for written description is insufficient.

Wang still further argues that Dr. Ketner recognized that Wang '680 incorporated Exhibits 1003 and 2038[20] into its teachings and that these Exhibits taught the specific deletion of ORF6, without any other E4 region being deleted (Paper 50, p. 7).

71. Gary Ketner, Ph.D., testified that Wang '680 (Ex 1031) referred to Bridge & Ketner 1989 (Ex 1003) and Bridge & Ketner 1990 (Ex 2038) at pages 12 and 10, respectively (Ex 2040, p. 11, ll. 8-10 and 17-22).

72. Wang '680 reads

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[20] Eileen Bridge and Gary Ketner (Bridge III), "Interaction of Adenoviral E4 and E1b Products in Late Gene Expression," Virology, Vo. 174, pp. 345-353 (1990) (Ex 2038).

> ... Since one of the E4 gene products [294R protein of open reading frame (ORF) 6] in association with the E1b gene product (496R protein) has a function of inhibiting cellular mRNA transport resulting in the cessation of cellular protein synthesis (***Bridge & Ketner, 1990***), the overexpression of the E4 gene region would be expected to ultimately result in cell death. [Ex 1031, p. 10, ll. 12-18, bold italics added.]
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> * * * * * *
>
> ... The mutant adenovirus, H5dl1014 [Bridge, et al, *Virology* **193**: 794-801 (1993)], was used to examine the complementing activity of the above described 293-E4 packaging cell line because it carries lethal deletions in the E4 region and can only grow in W162 cells (***Bridge, & Ketner, 1989***). [Id., p. 12, ll. 4-9, bold italics added.]

73. During cross-examination, Wang focused Dr. Ketner's attention on ΔE4 mutants 1001, 1002 and 1010 shown in Figure 1 of Bridge I (Ex 1003). Dr. Ketner stated that mutants 1001 and 1002 contained deletions in ORF6 and a part of ORF7, while mutant 1010 appeared to be deleted in just ORF6. [Ex 2040, p. 12, l. 19 - p. 14, l. 3.]

74. Of the twelve ΔE4 mutants depicted in Figure 1 of Bridge I (Ex 1003, p. 632), only two contained deletions in a single E4 ORF, i.e., dl1010 has a deletion in ORF6 only and dl1012 has a deletion in ORF6/7 only. The remaining mutants contain deletions in multiple E4 ORFs, e.g., dl1001 and dl1002 have deletions in ORFs 6 and 6/7, dl1003 contains deletions in ORFs 6, 6/7, 3/4 and 4, dl1005 has deletions in ORFs 1 and 2, and dl1007 has deletions in all seven E4 ORFs.

75. Figure 1 of Bridge III (Ex 2038, p. 347) depicts seven E1b and/or E4 deletion mutants. Mutants dl1006, dl1010 and dl1014 are said to have been previously described in "Bridge and Ketner, 1989," (Ex 1003) (Ex 2038, p. 346, c. 2, ¶ 2).

76. Dr. Ketner's attention was further focused on dl1010 in Bridge III. Consistent with his statement regarding dl1010 in Bridge I, Dr. Ketner acknowledged that dl1010 is a deletion of E4 ORF6 (Ex 2040, p. 14, l. 14 - p. 15, l. 4).

Based on the foregoing, Wang argues that "the Wang application does specifically teach the selective ORF6 mutation or deletion that Kovesdi insists is called for by the claims" (Paper 50, sentence bridging pp. 7-8).

However, incorporation by reference of Exhibits 1003 and 2038 does not convert the subject matter of Exhibits 1003 and 2038 into the invention of Wang '680. (Modine Mfg. Co. v. United States Int'l Trade Comm'n, 75 F.3d 1545, 1553, 37 USPQ2d 1609, 1614 (Fed. Cir. 1996), abrogated with respect to the doctrine of equivalents by Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd., 234 F.3d 558, 572, 56 USPQ2d 1865, 1875 (Fed. Cir. 2000) (en banc), "[I]ncorporation by reference does not convert the invention of the incorporated patent into the invention of the host patent.").

Second, Wang '680 does not specify what matter (i.e., which adenoviral deletion mutants) in Exhibits 1003 and 2038 is to be incorporated into Wang '680. See Ex parte Raible, 8 USPQ2d 1709, 1710 (Bd. Pat. App. & Int. 1988) (citing In re de Seversky, 474 F.2d 671, 177 USPQ 144, (CCPA 1973), "[t]he purpose of incorporation by reference in an application of matter elsewhere written down is for economy, amplification, or clarity of exposition, by means of an incorporating statement clearly identifying the subject matter which is incorporated and where it is to be found" (original emphasis)).

Thus, assuming without deciding that Wang '680 properly incorporates subject matter by reference to Bridge I and III (Exs 1003 and 2038), Wang '680 again does so without any "blaze marks" leading the skilled artisan to deletion of E4 ORF6 specifically. Indeed, Wang had to focus Dr. Ketner's attention on specific deletion mutants in Bridge I and III. While Bridge I and III describe various E4 deletion mutants, one of which

deletes only ORF6 (i.e., dl1010), these two Bridge references also disclose other mutants which do not entail deletion of ORF6 (e.g., dl1005). Furthermore, Wang has not explained how either Bridge reference points to the deletion of ORF6 as a feature, let alone a defining feature, of Wang's claimed adenoviral vector.

In view of the foregoing, we find nothing in the original disclosure of Wang '680 to indicate, explicitly or implicitly, that Wang had possession of the adenoviral vectors recited in Wang claims 52 and 54. Thus, Wang claims 52 and 54 are based on a specification which, as filed, does not satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

For the above reasons, Kovesdi preliminary motion 1 is **granted**.

VI. Wang preliminary motion 4

Wang moves pursuant to 37 CFR § 1.633(a) for judgment that Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 are unpatentable under 35 U.S.C. § 112, second paragraph, contending that the term "essential gene function" is indefinite and undefined (Paper 45). Kovesdi opposes (Paper 54); Wang replies (Paper 65).

According to Wang, the Kovesdi '416 specification describes replication defective adenoviral vectors in terms of deleted gene regions, not gene functions. Further according to Wang, the skilled artisan would understand the gene functions of a region to refer to all functions ultimately supplied by the region. Thus, the skilled artisan would require more information to identify the exact deletion(s) that will eliminate one gene function from a given region, while preserving other functions of that region. Still further according to Wang, the Kovesdi '416 specification does not describe which gene

functions are essential for what, and why. Finally, according to Wang, not only is it incumbent upon Kovesdi to define "essential gene function" since Kovesdi relied upon that term to overcome prior art, but also it is quite possible to do so as seen in a companion case which issued as U.S. Patent 5,851,806.

"The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, second paragraph. "The test for indefiniteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, Section 112 demands no more. The degree of precision necessary for adequate claims is a function of the nature of the subject matter." Miles Lab., Inc. v. Shandon, Inc., 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993) (internal citations omitted). The specification is "the single best guide to the meaning of a disputed term." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996). The court may also consider the prosecution history, if in evidence. Id. In summary, the Federal Circuit, in its own watershed decision in Markman, stated: "To ascertain the meaning of claims, we consider three sources: The claims, the specification, and the prosecution history." Markman v. Westview Instruments, Inc., 52 F.3d 967, 979, 34 USPQ2d 1321, 1329 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996).

A. As used in the Kovesdi '416 application, the term "essential gene function" refers to any function that is required for viral growth (i.e., a function that enables a replication-deficient adenoviral vector to replicate its genome, produce structural proteins and package the

viral genome).

77. Here, except for claim 19, all of the corresponding Kovesdi claims embrace adenoviral vectors "deficient in one or more essential gene functions of each of two or more adenoviral early regions" selected from the group consisting of E1, E2A and E4 regions of the adenoviral genome (see e.g., claims 36, 68 and 84).

78. Kovesdi did not define "essential gene function" per se in the '416 specification.

79. Kovesdi '416, as filed, states:

> Until now, adenoviral vectors used to express a foreign gene have been deficient in only a single early region (E1) that is essential for viral growth, i.e., singly functionally deficient. Only the essential region E1 or, alternatively, the nonessential region E3 has been removed for insertion of a foreign gene into the adenoviral genome. If the region removed from the adenovirus is essential for the virus to grow, a complementing system, such as a complementing cell line is necessary to compensate for the missing viral function. In other words, the complementing cell line will express the missing viral function so that the singly deficient adenovirus can grow inside the complementing cell. [Ex 1001, p. 8, ll. 21-34, emphasis added.]
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> * * * * * *
>
> The present invention provides, among other things, multiply deficient adenoviral vectors for gene cloning and expression. The multiply deficient adenoviral vectors of the present invention differ from currently available singly deficient adenoviral vectors in being deficient in at least two essential gene functions and in being able to accept and express larger pieces of foreign DNA. [Id., p. 11, ll.12-19, emphasis added.]
>
> * * * * * *
>
> Preferably, the adenoviral vector of the present invention is at least deficient in a function provided by early region 1 (E1) and/or one or more functions encoded by early region 2 (E2), such as early region 2A (E2A) and early region 2B (E2B), and/or early region 3 (E3), and/or early region 4 (E4) of the adenoviral genome (id., p. 11, ll. 26-31, emphasis added).
>
> * * * * * *
>
> In addition, the present invention also provides complementing cell lines for propagation of the present inventive multiply deficient adenoviral vectors. The preferred cell lines of the present invention are characterized in complementing for at least one gene function of the gene functions comprising the E1, E2, E3 and E4 regions of the adenoviral

genome. [Id., p. 13, ll. 27-33, emphasis added.]

* * * * * *

The complementing cell line must be one that is capable of expressing the products of the two or more deficient adenoviral gene functions at the appropriate level for those products in order to generate a high titer stock of recombinant adenoviral vector (id., p. 14, ll. 18-22, emphasis added).

80. While originally filed Kovesdi claims embraced adenoviral vectors "deficient in two or more adenoviral gene functions," none of the originally filed claims referred to "essential" gene functions.[21]

81. Rather, originally filed Kovesdi claims 8 and 9 recited that the vector "only functions in a complementing cell line" (Ex 1001, pp. 36-37).[22]

82. Dr. Ketner testified for Kovesdi that

[t]he terms "complementation" and "complementing" were understood in 1994, and continue to be understood, by those of ordinary skill in the art to refer to, in the context of adenovirology, the ability of a helper virus or a cell line to supply the necessary adenoviral proteins to enable the production of viral particles. That is, a complementing cell line, for example, will supply adenoviral proteins that enable the replication-

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[21] See e.g., originally filed Kovesdi claims 1, 2 and 5 (Ex 1001, p. 36):

1. An adenoviral vector that is deficient in two or more adenoviral gene functions.

2. The adenoviral vector of claim 1, wherein at least one of the said two or more gene functions is selected from the group of gene functions comprising the E1, E2, E3 and E4 regions of the adenoviral genome.

5. The adenoviral vector of claim 1, wherein the said two or more adenoviral gene functions is all the adenoviral gene functions.

[22] Originally filed Kovesdi claims 8 and 9 read:

8. The adenoviral vector of claim 1, wherein said adenoviral vector only functions in a complementing cell line.

9. The adenoviral vector of claim 8, wherein said adenoviral vector only functions in a complementing cell line as a result of the modification of adenoviral inverted terminal repeats or packaging signal.

deficient adenoviral vector to replicate its genome, produce structural proteins, and package the viral genome. Thus, viral particle (i.e., virion) production and "complementation" are not mutually exclusive events, as the term "complementation" was and is understood to encompass all of the events required to generate an intact adenovirus particle (i.e., virion). [Ex 1024, ¶ 7, emphasis added.]

83. Dr. Ketner further testified that

> At the time of the filing of the Kovesdi '416 application, the terms "gene function" and "region" were known in the art of virology. The term "gene function" references an activity of a viral gene product. The term "region" refers to the location of particular DNA sequences within a viral genome that can be designated by base pairs or map units. The terms "gene function" and "region" were used in the Kovesdi '416 application in a conventional manner with their respective usual meanings.
>
> At the time of the filing of the Kovesdi '416 application, the term "essential gene function" was known in the art of virology to refer to any function that is required for viral growth (e.g., a function necessary for viral replication, propagation, or packaging). A deficiency in an essential gene function renders a virus unable to produce infectious virions unless complementation of the missing activity (e.g., by a complementing cell line or helper virus) is provided. The meaning of the term "essential gene function" is particularly clear in the context of the Kovesdi '416 application inasmuch as that application pertains to replication-deficient adenoviral vectors and complementing cell lines therefor (EXHIBIT 1001, page 1, lines 8-10). Thus, in the context of the Kovesdi '416 application as filed, one of ordinary skill in the art would have understood this to be the meaning of the terms "essential gene function." [Ex 1039, ¶¶ 4-5.]

See also Ex 1004, p. 25, ll. 10-21 ("an essential function would be generally understood to be a function which is required for the virus to be propagated", although "[i]t's somewhat context sensitive", e.g., "in different environments, different genes are essential").

84. Dr. Curiel testified similarly for Wang that "gene function is understood to reference the activity of different RNA and protein species encoded within a given gene region. In contrast, 'gene region' refers to the location of particular DNA sequences

within an adenoviral genome and can be designated by base pair or map unit coordinates" (Ex 2012, ¶ 40).

85. Dr. Curiel further testified that a deficiency, in terms of a vector deficiency, "would be a deficiency of a gene or gene function that is required for a full propagated cycle" (Ex 1040, p. 50, l. 17 - p. 51, l. 2). In other words, when Dr. Curiel says "gene or gene function, ... [he means] the product of the gene that contributes to the fully realized propagated viral infection that yields useful amounts of vector" (id., p. 51, l. 19 - p. 52, l. 1).

86. More specifically, Dr. Curiel testified

> A: A good way to understand the term "essential gene" would be to consider the use of its antipode which is nonessential gene, so E3 is described as a nonessential gene whereas, to look at it another way, when the adenovirus infects the cell, it wants to do three things. It wants to take over the host machinery to manufacture its proteins. It wants to take over the host machinery to replicate its genome and it wants to avoid immune eradication while that's happening, and E3 prevents immune eradication. That has nothing to do with replication of new virion production, so the term "nonessential" was ascribed to E3 because it wasn't related to replication of new virion production. It was very essential for the virus to live and lateralize in animals, but it had nothing to do with vectorologists manipulating viruses and propagating them in the laboratory.
>
> So that by understanding, essential gene is that which has to do with the ability to allow a viral replicative event and new virus production.
>
> Q: And by extension, was it also understood that essential gene function related to the function of the gene to allow for viral replication?
>
> A: Yes, with the caveat that the embodied ambiguity is whatever that was. We didn't always know what the functions were.

Based on the foregoing, one skilled in the art reading Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 in light of Kovesdi '416 would not have found the

term "essential gene function" is indefinite. Rather, the skilled artisan would have understood the term "essential gene function" to refer to any function that is required for viral growth (i.e., a function that enables a replication-deficient adenoviral vector to replicate its genome, produce structural proteins and package the viral genome).

B. The prosecution history is consistent with the understanding that "essential gene function" relates to a function of the gene that allows for viral replication.

87. The examiner rejected originally filed Kovesdi claims 8 and 9 as indefinite because "it is unclear exactly what is intended when the vector 'functions' in a complementing cell line - for example, replication, gene expression, or perhaps viral packaging" (Ex 2010, p. 6, ¶ 2).

88. The examiner further rejected originally filed Kovesdi claims 1-8, 10-17, 20-21 and 24 as anticipated by Gregory et al. and claims 1, 2, 4, 8, 10, 11, 13, 17, 20, 21 and 24 as anticipated by Rosenfeld et al. (Ex 2010, pp. 6-8).

89. In a responsive amendment filed May 13, 1996, Kovesdi cancelled a number of originally filed claims and replaced them with vector and complementing cell line claims "specifying that the adenoviral vector is deficient in one or more essential gene functions in each of two or more adenoviral early regions selected from the group consisting of the E1, E2A, and E4 regions" (Ex 2013, p. 12).

90. According to Kovesdi, the rejection of claims 8 and 9 under § 112, second paragraph, was moot in view of the cancellation of these claims (Ex 2013, p. 18).

91. Further according to Kovesdi, its newly claimed vectors and complementing cell lines are not anticipated by Gregory et al. because

> the vectors of Gregory et al. are not "deficient in one or more essential gene functions in each of two or more adenoviral early regions selected from the group consisting of the E1, E2A, and E4 regions of the adenoviral genome," but rather are merely deficient in E1 gene functions and nonessential E4 gene functions. Thus, the so-called E1$^-$ E4$^-$ vectors of Gregory et al. retain ORF6 ... thereby retaining the essential gene function of E4 and enabling the vectors to be propagated in the 293 cell line which only complements for E1 gene function deficiencies. [Ex 2013, p. 19, original emphasis.]

92. Kovesdi '416 expressly states that "ORF-6 is the only absolutely essential E4 product necessary for virus growth in a non-E4 complementing cell line" (Ex 1001, p. 28, ll. 10-12).

93. Still further according to Kovesdi, its newly claimed vectors and complementing cell lines are not anticipated by Rosenfeld et al. for the same reasons as discussed for Gregory et al. (Ex 2013, p. 21).

Therefore, the prosecution history is consistent with the understanding that "essential gene function" relates to a gene function that allows for viral replication.

C. The addition of information to another patent application, even if related as a continuation-in-part, does not constitute an admission that the original application was lacking in some respect.

94. U.S. Patent 5,851,806 ("the '806 patent") issued December 22, 1998 based on application 572,126, filed December 14, 1995. It is a continuation-in-part of PCT application PCT/US95/07341, filed June 7, 1995, which is a continuation-in-part of the involved Kovesdi '416 application. [Ex 2031, front page.]

Addition of an explicit definition of "a deficiency in a gene or gene function" in the '806 patent does not create a presumption that Kovesdi acquiesced in the merits of any rejection of the claims in the Kovesdi '416 application. Paperless Accounting, Inc. v.

Bay Area Rapid Transit System, 804 F.2d 659, 663-64, 231 USPQ 649, 652 (Fed. Cir. 1986), cert. denied, 480 U.S. 933 (1987).

D. The enablement and written description requirements of § 112, first paragraph, are separate and distinct issues from the definiteness requirement of § 112, second paragraph.

Allegations that one of ordinary skill in the art was not capable of manipulating the adenoviral genome so as to delete one or more essential gene functions of two or more regions selected from the group consisting of the E1, E2A and E4 regions of the adenoviral genome and that the Kovesdi '416 application does not contain an adequate written description of the subject matter of Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 are woven throughout Wang preliminary motion 4.

Allegations of lack of enablement and inadequate written description are properly presented in the context of a motion regarding unpatentability under 35 U.S.C. § 112, first paragraph. Such allegations say nothing about a skilled artisan's understanding of the bounds of the Kovesdi claims at issue and, therefore, are tangential, if not irrelevant, to the definiteness of the term "essential gene function."

E. Wang's contingent request for a judgment of no interference-in-fact as to Kovesdi claim 19 is moot.

Wang contends that if Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 are found unpatentable, none of the Wang claims create either "an expectancy of those skilled in the art of the desirability of the specific embodiment of Kovesdi Claim 19, ... [or] a reasonable expectancy ... that the specific embodiment of Kovesdi Claim 19 will be effective" (Paper 45, p. 19). Thus, contingent on the grant of Wang preliminary motion 4, Wang requests that this interference be terminated for want of an

interference-in-fact (id.). In view of our denial of Wang preliminary motion 4, we need not address this "contingent" motion.

In summary, Wang has not satisfied its burden of establishing that one skilled in the art would not have understood the term "essential gene function(s)" as recited in Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 when read in light of the Kovesdi '416 specification. For the above reasons, Wang preliminary motion 4 is **denied**.

VI. Wang preliminary motion 3

Wang moves pursuant to 37 CFR § 1.633(a) for judgment that Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 are unpatentable under 35 U.S.C. § 112, first paragraph (as not being adequately described) (Paper 44). Kovesdi opposes (Paper 53); Wang replies (Paper 64).

Wang contends that the aforementioned Kovesdi claims "fail to comply with the written description requirement ... as the term 'essential gene function(s)' ... is not supported by any written description" (Paper 44, sentence bridging pp. 8-9). Wang further contends that "[n]either the term ['essential gene function'], nor the legal equivalent of the term, appears anywhere in the in the specification of the involved Kovesdi '416 application as originally filed" (id., p. 9, ¶ 1).

Wang preliminary motion 3 is **denied** for substantially the same reasons as given above in regard to Wang preliminary motion 4. Furthermore, the definiteness and enablement requirements under 35 U.S.C. § 112, first and second paragraphs, respectively, are separate requirements from the written description requirement of 35 U.S.C. § 112, first paragraph. Finally, Wang's "contingent" request for a judgment of no

interference-in-fact between Wang's claims and Kovesdi claim 19 (Paper 44, p. 14) is moot.

VII. Wang preliminary motion 2

Wang moves pursuant to 37 CFR § 1.633(a) for judgment that Kovesdi claims 20-21, 24-26, 36-87 and 89-95 [sic 89-90 and 92-95][23] are unpatentable under 35 U.S.C. § 112, first paragraph (as not being enabled by the specification) (Paper 43). Kovesdi opposes (Paper 52); Wang replies (Paper 63).

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting from In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These factors are neither mandatory nor cumulative. Enzo Biochem Inc. v. Calgene, Inc., 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999). "[A]pplication sufficiency under § 112, first paragraph,

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[23] Kovesdi claim 91 has does not correspond to any of Counts 1 through 6 and, therefore, is not involved in this interference.

must be judged as of its filing date." In re Glass, 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). "Tossing out the mere germ of an idea does not constitute an enabling disclosure ... reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech, 108 F.3d at 1366, 42 USPQ2d at 1005.

A. Nature of the invention

95. The Kovesdi '416 specification "relates to recombinant, multiply deficient adenoviral vectors and complementing cell lines and to the therapeutic use of such vectors" (Ex 1001, p. 1, ll. 8-10).

B. Breadth of the claims

Pending application claims are given the broadest reasonable interpretation consistent with applicant's specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). The reason is simply that an applicant in the PTO has an opportunity to amend its claims. For example, during an interference proceeding, in response to an unpatentability motion brought by an opposing party pursuant to 37 CFR § 1.633(a), an applicant can not only oppose the unpatentabilty motion, but also amend its application claim(s) corresponding to a count pursuant to 37 CFR §§ 1.633(i) and (c).

Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 fall into three groups -- (1) adenoviral vector claims 20-21, 24-26 and 52-83; (2) complementing cell line claims 36-51, 89-90 and 92-95; and (3) method of making adenoviral vector claims 84-87.

(1) adenoviral vector claims 20-21, 24-26 and 52-83

Kovesdi claims 20-21, 24-26 and 52-83 recite adenoviral vectors which specify

certain minimum deficiencies in essential early gene functions.

Claim 68[24] and its dependent claims 69-83 encompass adenoviral vectors deficient in all but "one functional early or one late region genes."

Claims 20-21, 24-26 and 52-67 similarly encompass adenoviral vectors which specify certain minimum deficiencies in essential early gene functions. Unlike claims 68-83, claims 20-21, 24-26 and 52-67 do not require the presence of "one functional early or one late region genes" and, therefore embrace adenoviral vectors deficient in all functional early and late region genes. Claims 20-21, 24-26 and 52-67 further require that the vector be grown in particular complementing cell lines, i.e., the cell lines described in claims 36-51. While the patentability of a product-by-process claim is based upon the product itself, product-by-process claims must be analyzed to determine what effect, if any, the recited process of preparation has on the structure, composition or properties of the claimed product. In re Thorpe, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985). Since a complementing cell line provides missing gene functions in *trans*, claims 20-21, 24-26 and 52-67 exclude a vector having a deletion which requires complementation in *cis*.

96. All that is required in *cis* are the inverted terminal repeats ("ITRs") and a packaging sequence (Ex 1012, p. 621, c. 2, ¶3).

Therefore, Kovesdi claims 20-21, 24-26 and 52-67 encompass vectors wherein essentially the entire genome has been removed, except for the ITRs and a packaging

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[24] Kovesdi claim 68 reads: An adenoviral vector that is deficient in one or more essential gene functions in each of two or more adenoviral early regions selected from the group consisting of the E1, E2A, and E4 regions of the adenoviral genome, wherein said vector comprises one or more functional early or late region genes (FF 23).

sequence.

None of Kovesdi claims 20-21, 24-26 and 52-83 are limited to with respect to any particular type or subtype of adenovirus, adenoviral DNA or adenoviral vector.[25]

The above claim interpretation is consistent with the teachings of Kovesdi '416.

97. For example, according to the Kovesdi '416 specification,

> [a]ny subtype, mixture of subtypes, or chimeric adenovirus may be used as the source of DNA for generation of the multiply deficient adenoviral vectors. However, given that the Ad5 genome has been completely sequenced, the present invention will be described with respect to the Ad5 serotype. [Ex 1001, p. 11, ll. 20-25.]
>
> * * * * * *
>
> [t]he present invention, however, is not limited to adenoviral vectors that are deficient in gene functions only in the early region of the genome. Also included are adenoviral vectors that are deficient in the late region of the genome, adenoviral vectors that are deficient in the early and late regions of the genome, as well as vectors in which essentially the entire genome has been removed, in which case it is preferred that at least either the viral inverted terminal repeats and some of the promoters or the viral inverted terminal repeats and a packaging signal are left intact. [Id.,

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[25] The following passage is taken from MEDICAL VIROLOGY, fourth edition, White and Fenner (eds.), Academic Press, San Diego (1994), pp. 306-309 at p. 308 (copy enclosed):

Classification

Mammalian and avian adenoviruses comprise two distinct genera, designated *Mastadenovirus* and *Aviadenovirus*, respectively. In turn, the genus *Mastadenovirus* comprises numerous adenovirus serotypes specific for particular mammalian species. Currently, 47 serotypes of human adenovirus (sometimes designated h-Ad1 to h-Ad47) are recognized. They are assigned to six subgenera (A-F) on the basis of various biochemical and serological criteria which generally match up quite well with previous assignments on the basis of certain biological characteristics, notably oncogenicity and hemagglutination (Table 19-2). Members of subgenus A were found to be highly oncogenic for baby rodents and subgenus B less so, and the six subgenera are also compatible with the earlier subdivision based on agglutination of rat or monkey red cells and with the degree of homology of the genomes.

Designation as a distinct serotype is based on a serological difference (of >16-fold) in reciprocal neutralization assays. The fiber protein is responsible for hemagglutination and is type-specific, whereas the hexon protein carries genus-specific, subgenus-specific, intertype-specific, and type-specific epitopes and, like the fiber, elicits neutralizing antibodies. Numerous isolates from AIDS patients have proved difficult to type, as they share epitopes with the fiber and/or hexon proteins of one or more distinct serotypes. Nucleic acid sequencing should reveal whether these so-called intermediate strains have arisen by mutation or by recombination.

p. 12, ll. 3-13.]

Thus, we interpret Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 as broadly as the language in the Kovesdi '416 specification would have been reasonably understood by one of ordinary skill in the art as of its filing date, June 10, 1994. We reject Kovesdi's argument that its claims are narrowly drawn, i.e., that its "claims 20-26 and 52-83, specify that the ... vector is deficient in one or more essential gene functions in each of two or more of the E1, E2A, and/or E4 regions ... not ... that the ... vector is deficient in an essential gene region of any other region" (Paper 53, p. 18). As explained above, Kovesdi's vector claims are not so limited and include, e.g., vectors requiring complementation of E2B, MLP, any one or more of L1-L5, and VA-RNA, in addition to the gene regions explicitly recited in these claims.

(2) complementing cell line claims 36-51, 89-90 and 92-95

98. The complementing cell line of claims 36-51 and 95 are all derived from HEK [human embryonic kidney] 293 or A549 cells.[26]

99. The complementing cell line of claim 90 is derived from a human embryonic kidney cell and is, therefore, broader than a cell line derived from HEK 293 cells

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[26] A "cell line" is a population of cells cultured in vitro that are descended through one or more generations (and possibly sub-cultures) from a single primary culture. The cells of such a population share common characteristics. "Derive" means to obtain a new cell line from an existing cell line such that the new cell line has at least one property added or deleted from the properties of the existing parent cell line. A "primary cell line" is a cell line developed by isolating cells directly from an organism and culturing a single cell type. Primary cell lines are typically terminally differentiated, i.e., structurally and functionally developed into a specific cell type. For example, the HEK "293 cell line" is a permanent cell line derived from primary human embryonic kidney cells which have been transformed by sheared human adenovirus adenovirus type 5 (Ad 5) DNA. HEK 293 cells are commercially available from the American Type Cell Culture collection, item no. ATCC CRL-1573. [Glossary, pp. 1-3 and 7.] HEK 293 cells contain and express the complementing adenoviral E1 region (Ex 1001, p. 9, ll. 18-19).

specifically.

100. The complementing cell lines of claims 89 and 92-94 are not limited to derivation from any specific parental cell line.

101. According to the Kovesdi '416 specification,

> .. the present invention also provides complementing cell lines for propagation of the present inventive multiply deficient adenoviral vectors. The preferred cell lines of the present invention are characterized in complementing for at least one gene function of the gene functions comprising the E1, E2, E3 and E4 regions of the adenoviral genome. Other cell lines include those that complement adenoviral vectors that are deficient in at least one gene function from the gene functions comprising the late regions, those that complement for a combination of early and late gene functions, and those that complement for all adenoviral functions. [Ex 1001, p. 13, l. 27 - p. 14, l. 3.]

(3) method of making adenoviral vector claims 84-87

102. Kovesdi method claims 84-87 comprise methods of propagating ΔE1ΔE2A or ΔE1ΔE4 or ΔE2AΔE4 defective adenoviral vectors in cells "wherein said nucleic acid sequences in said cell that complement for said essential functions of said E2A and E4 regions of the adenoviral genome are operably linked to inducible promoters."

103. Claim 84 is open to any inducible promoter. Claims 85-87 specify that the inducible promoter is a sheep metallothionine promoter, a promoter of the tetracycline expression system and a promoter of a lac expression system, respectively.

104. The complementing cell of claims 84-87 are not limited to derivation from any specific parental cell line.

Since complementing cell lines provide missing gene functions in *trans*, claims 84-87 encompass making adenoviral vectors wherein essentially the entire genome has been removed, except for the ITRs and a packaging sequence.

C. Level of skill in the art

The level of skill in the art is relatively high as evidenced by the prior art of record. A person of ordinary skill in the art would be knowledgeable in adenovirus biology, adenoviral vectors and adenoviral vector complementation systems.

D. State of the prior art

1. knowledge of the Ad2 and Ad5 adenoviral genome was extensive

By 1992, knowledge of the adenovirus genome was extensive, including the viral life cycle, DNA replication, transcription and RNA processing, and regulation of virus gene expression. [See e.g., Ex. 1010, ¶ 5 and examples of prior art of record.[27]]

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[27] Examples of Prior Art include:

1963: Green et al., "Biochemical Studies on Adenoviral Multiplication. IV. Isolation, Purification, and Chemical Analysis of Adenovirus," Virology, Vol. 20, pp. 199-207 (Ex 1045).

1977: D. Klessig, "Isolation of a Variant of Human Adenovirus Serotype 2 That Multiplies Efficiently on Monkey Cells," Journal of Virology, Vol. 21, No. 3, pp. 1243-1246 (Ex 1052).

Graham et al., "Characteristics of a Human Cell Line Transformed by DNA from Human Adenovirus Type 5," Journal of General Virology, Vo. 36, pp. 59-74 (Ex 1006).

1980: Bridge III, "Interaction of Adenoviral E4 and E1b Products in Late Gene Expression" (Ex 2038).

1983: Weinberg et al., "A cell line that supports the growth of a defective early region 4 deletion mutant of human adenovirus type 2," Proc. Natl. Acad. Sci. USA, Vol. 80, pp. 5383-5386 (Ex 2019).

1984: J. Sussenback, "The Structure of the Genome," Chapter 3, pp. 35-124, in THE ADENOVIRUSES, (Ginsberg, ed.) (New York: Plenum Press) (Ex 1013).

Klessig et al., "Introduction, Stable Integration, and Controlled Expression of a Chimeric Adenovirus Gene Whose Product is Toxic to the Recipient Human Cell," Molecular and Cellular Biology, Vol. 4, No. 7, pp. 1354-1362 (Ex 1008).

1985: Rice et al., "Isolation and Analysis of Adenovirus Type 5 Mutants Containing Deletions in the Gene Encoding the DNA-Binding Protein," Journal of Virology, Vol. 56, No. 3, pp. 767-778 (Ex 1004).

Halbert et al., "Adenovirus Early Region 4 Encodes Functions Required for Efficient DNA Replication, Late Gene Expression, and Host Cell Shutoff," Journal of Virology, Vol. 56, No. 1, pp. 250-257 (Ex 1021).

1987: Cutt, "Analysis of Adenovirus Early Region 4-Encoded Polypeptides Synthesized in Productively Infected Cells," (Ex 1022).

Falgout et al., "Adenovirus Early Region 4 Is Required for Efficient Virus Particle Assembly," Journal of Virology, Vol. 61, No. 12, pp. 3759-3768 (Ex 1041).

1988: McGrory et al., "SHORT COMMUNICATIONS: A Simple Technique for the Rescue of Early Region 1 Mutations into Infectious Human Adenovirus Type 5," Virology, Vol. 163, pp. 614-617 (Ex 2005).

K. Berkner, "Development of Adenovirus Vectors for the Expression of Heterologous

105. Dr. Ketner testified that the genomes of the most characterized adenoviruses, human serotype 2 (Ad2) and 5 (Ad5), were "quite similar" with "virtually identical" locations for the open reading frames or coding sequences (Ex 1010, ¶ 7).

106. According to Kovesdi '416, "[t]he overall organization of the adenoviral genome is conserved among serotypes, such that specific functions are similarly positioned" (Ex 1001, p. 3, ll. 18-20).

2. "singly-deficient" adenoviral vectors were known

107. The first generation of replication-defective adenoviral vectors deleted the E1 region (and optionally the nonessential E3 region) from the adenoviral genome and replaced it with a foreign gene of interest or transgene. Without E1A there is no transcription of the rest of the early genes, thereby preventing viral replication. Such

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Genes," BioTechniques, Vol. 6, pp. 616-618, 620-624, 626, 628, 629 (Ex 1012).

1989: Ketner et al., "Complementation of adenovirus E4 mutants by transient expression of E4 cDNA and deletion plasmids," Nucleic Acids Research, Vol. 17, No. 8, pp. 3037-3048 (Ex 1002).

Mautner et al., "Complementation of Enteric Adenovirus Type 40 for Lytic Growth in Tissue Culture by E1B 55K Function of Adenovirus Types 5 and 12," Virology, Vol. 171, pp. 619-622 (Ex 1036).

1989: Bridge I, "Redundant Control of Adenovirus Late Gene Expression by Early Region 4," (Ex 1003).

1990: Gilardi et al., "Expression of human α_1-antitrypsin using a recombinant adenovirus vector," FEBS, Vol. 267, No. 1, pp. 60-62 (Ex 2023).

1992: Brough et al., "Construction, Characterization, and Utilization of Cell Lines Which Inducibly Express the Adenovirus DNA-Binding Protein," Virology, Vol. 190, pp. 624-634 (Ex 2008).

Rosenfeld et al., "In Vivo Transfer of the Human Cystic Fibrosis Transmembrane Conductance Regulator Gene to the Airway Epithelium," Cell, Vol. 68, pp. 143-155 (Ex 2022).

1993: Roovers et al., "Analysis of the Adenovirus Type 5 Terminal Protein Precursor and DNA Polymerase by Linker Insertion Mutagenesis," Journal of Virology, Vol. 67, No. 1, pp. 265-276 (Ex 1015).

Bridge II, "Adenovirus Early Region 4 and Viral DNA Synthesis," (Ex 1030).

Kozarsky et al., "Adenovirus-Mediated Correction of the Genetic Defect in Hepatocytes from Patients with Familial Hypercholesterolemia," Somatic Cell and Molecular Genetics, Vol. 19, No. 5, pp. 449-458 (Ex 1054).

1994 (May): Yang et al., "Cellular immunity to viral antigens limits E1-deleted adenoviruses for gene therapy," Proc. Natl. Acad. Sci. USA, Vol. 91, pp. 4407-4411 (Ex 2036).

WO 94/12649 "Gene Therapy for Cystic Fibrosis," published **June 9, 1994**, (using adenovirus-based vectors) (Ex 2024).

vectors are capable of infecting a cell only once and no viral propagation occurs. [Ex 1001, p. 8; Ex 1012, pp. 616-620; Ex 2037, p. 129.]

108. The problem with singly-deficient adenoviral vectors, as recognized by Kovesdi,

> is that they limit the amount of usable space within the adenoviral genome for insertion and expression of a foreign gene. Due to similarities, or overlap, in the viral sequences contained within the singly deficient adenoviral vectors and the complementing cell lines that currently exist, recombination events can take place and create replication competent viruses within a vector stock. This event can render a stock of vector unusable for gene therapy purposes as a practical matter. [Ex 1001, ¶ bridging pp. 9-10.]

109. As of 1994, "the adenoviruses that have been used in gene therapy protocols fall into the type C nononcogenic group of adenoviruses. Adenovirus types 2 and 5 are the prototypical viruses within this group." [Ex 2037, p. 129, c. 2, ¶ 1.]

3. adenoviral vectors lacking essential gene function must be grown by complementation

Since replication-defective adenoviral vectors lack essential gene function, the products of the missing gene(s) must be supplied by a source other than the viral genome. Complementation by one of two methods is possible – use of complementing cell lines or use of helper viruses.

a. use of a helper virus results in a mixed viral stock of viral vector and helper virus

110. Replication-defective adenoviral vectors can be grown using a helper virus, e.g., a wild-type adenovirus or an Ad2-simian virus 40 hybrid. (Ex 1041, p. 3759, c. 2, last ¶; Ex 1012, p. 621, ¶ bridging cc. 2-3).

111. Indeed, Dr. Curiel testified that the only way to complement for all early and late gene regions, defective ITRs and packaging sequences would be to use a helper virus

(Ex 2012, ¶ 14).

112. However, "a defective mutant grown in the presence of replication-competent helper virus tends to disappear from the stock as any cell infected by such a mutant alone yields no progeny, whereas cells singly infected by the helper produce a normal yield of virus particles" (Ex 2017,[28] p. 26, § 1.1).

113. WO 94/12649 (Gregory WO '649), published one day before the June 10, 1994 filing date of Kovesdi '416, suggested using a packaging defective helper virus, e.g., a virus with mutations in its packaging sequence or a virus with a genome size greater than approximately 37.5 kb, to increase the proportion of adenoviral vector in viral preparations made using a helper (Ex 2024, p. 53, l. 34 - p. 54, l. 3).

114. As late as 1999, the art taught that a helper virus "should have no properties that make low levels of contamination of the eventual purified mutant stock unacceptable, as no physical purification scheme is completely effective" (Ex 2017, p. 26, § 1.2).

b. use of complementary cell lines for singly-deficient adenoviral vectors was known

115. Dr. Kovesdi testified that the HEK 293 cell line, which complements for E1 deficiencies, has been the "mainstay of adenoviral research for about 20 years" (Ex 2009, ¶ 8). Dr. Kovesdi further testified that cell lines complementing for single mutations in E2A and E4, i.e., gmDBP and W162 cells (generated from HeLa and Vero parental cell lines, respectively), have been known since 1984 and 1983 (id., ¶ 9).

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[28] Ketner et al., "Isolation, Growth, and Purification of Defective Adenovirus Deletion Mutants," pp. 25-32, in METHODS IN MOLECULAR MEDICINE, Vol. 21: Adenovirus Methods and Protocols, W.S.M. Wold (ed.), Humana Press Inc., Totowa, NJ (1999) (Ex 2017).

116. Dr. Ketner testified that parental cell lines used to generate complementing cell lines prior to 1994 included 293 cells, A549 cells, HeLa cells and Vero cells (Ex 1039, ¶ 12). (See also Exs 1006-1008.)

E. Predictability or unpredictability of the art

1. the actual deletion of genetic material was predictable

117. Wang's expert, Dr. Curiel, testified that "[t]he actual deletion of genetic material from an adenoviral genome is probably the most predictable aspect and probably consistent with standard techniques and amenable to standard methods" (Ex 1040, p. 48, ll. 7-12).

118. Dr. Curiel further testified that

> [i]n 1994, those of ordinary skill in the field of recombinant adenoviral vectors, would readily characterize the state of the art as unpredictable, both with respect to the effect deletion or mutations may have on the vector and the corresponding requirements necessary for the propagation and rescue of a recombinant vector provided by a supporting cell line. In developing a recombinant vector or supporting cell line one of skill would be hopeful of success, but success in this field was, and remains empiric. There would be no expectation of success for a unique vector or cell line based on the reported success of another. Historically, failed vectors are the rule, not the exception. [Ex 2012, ¶ 30.]

2. expression of an appropriate level of missing gene product in a temporal pattern consistent with that seen in normal wild-type viral infection of a cell presents a major problem

119. Dr. Kovesdi testified that

> there are a large number of structural and regulatory genes that are temporally regulated within the adenoviral genome. Deleting or disrupting one of these genes, and/or providing the missing gene product in *trans* in an inappropriate temporal pattern, level of production, or form, can cripple virus replication by resulting in either minimal or an absence of functional complementation .... [Ex 2009, ¶ 10, citations omitted.]

120. Both parties agree that

> [a]s explained by Dr. Kovesdi, reasons for the difficulty in obtaining complementing cell lines abound. Among them Dr. Kovesdi includes that there is *no means of selecting for cells that might contain DNA sequences that might support the growth of a particular adenoviral vector.* (Exhibit 2009, ¶10; emphasis supplied). Thus, success with viral replication or packaging into virions in a particular cell line is empiric and cannot be predicted or otherwise identified. (Exhibit 2012, ¶9).

(See Paper 53, p. 1 where Kovesdi admits Wang fact 10 as set forth in Paper 44, p. 4.)

a. the structure/sequence/function relationships mapped by the highly homologous subgroup C serotypes Ad2 and Ad5 has not been show to be reasonably predictive of structure/sequence/function relationships in other human subgroups, in other mammals or in birds

121. According to Dr. Curiel, research on Ad2 and Ad5 human adenovirus serotypes is not predictive for creating recombinant adenoviruses using the genome of non-Ad2/5 viruses (Ex 2012, ¶ 20).

122. Dr. Ketner disagrees. According to Dr. Ketner,

> one of ordinary skill in the art had the knowledge and ability to use the teachings of the Kovesdi '416 application to prepare and complement for non-serotype 2 or 5 adenoviral vectors and even non-human adenoviral vectors. Some variability exists between adenovirus of different serotypes. However, the "unpredictable" differences would not substantially affect the use of different adenoviral serotypes for the purposes described in the Kovesdi '416 application. All that would be required of the ordinarily skilled artisan would be to locate major features of the adenoviral genome (e.g., early regions or late regions). This could be accomplished using standard methods and, because the genome architecture of adenoviruses is well conserved, would be fairly routine and unlikely to involve any problems requiring undue experimentation. [Ex 1039, ¶ 13.]

Dr. Ketner did not identify any evidence of record to support his bald assertion that the adenoviral genome architecture is so well conserved that no undue

experimentation would be involved in identifying major features, e.g., from different serotypes or different species.

123. Rather, serotypes Ad2 and Ad5 belong to human adenoviral subgroup C. "In general, members of the same subgroup have genomes that are homologous for more than 90%. However, members of subgroup A share only 48-69% of their DNA sequences. The homology among members of different subgroups is less than 20% (Table 1)." [Ex 1013, p. 37, ¶ 2.] According to Table 1 of Sussenbach, there is a 99-100% DNA homology within subgroup C, but only a 4-23% DNA homology between subgroup E and the other subgroups (id., p. 38).

124. Moreover, when Dr. Ketner was asked if one gene function could be selectively ablated while another was retained, he replied that the region required for the function would have to be identified by genetic analysis and then smaller and smaller deletions would be made within the identified region to see their impact. In other words, it is generally unpredictable which gene functions can or cannot be separated by selective ablation without undertaking individual genetic analyses. [Ex 1044, p. 19, l. 2 - p. 21, l. 3.[29]]

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[29] Dr. Ketner testified:

A: Well, you identify the regions required for each of these functions by genetic analysis, and that's been done, and then you make either point mutations or small deletion mutants in the region responsible for one function, and depending on the specific properties of system, these sorts of the mutations can sometimes separate functions.

Q: Is it -- it's sometimes the case that you can separate functions and sometimes not that case?

A: That's correct.

Q: Had the genetic analysis necessary to separate the two functions you identified [i.e., the E4-34k and E1b-55k proteins] been done by 1994 for any of the adenovirus serotypes?

Therefore, to the extent the testimony of Dr. Curiel conflicts with that of Dr. Ketner, we credit the former over the latter. While some arguments for predictability might be made based on a high degree of structural or sequence homology within subgroup C or even arguably between other human adenoviral subgroups, the structure/sequence/function relationships mapped by the highly homologous human serotypes Ad2 and Ad5 of subgroup C has not been shown to be reasonably predictive of structure/sequence/function relationships in other subgroups, mammals or birds.

125. Indeed, as of 1997, there were no published reports describing construction of a non-subgroup C replication-defective adenoviral vector (Ex 2021, p. 8946, c. 2, ¶ 2).

3. providing complementing cell lines that enable propagation of multiply-deficient adenoviruses is unpredictable

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A: I believe that the functions which I just described had not been separated by mutation in 1994.
I'll qualilfy that by saying I'd actually have to go look, because I'm not certain of the dates, but I believe that's the case.

Q: How do you -- in the kind of a gross mechanistic framework, how do you perform that genetic analysis?

A: If you were interested in analyzing the particular functions of a specific protein, you would frequently start out by deleting the entire genic [sic] code and the entire protein, and asking for phenotypes that deletion conferred.
You would search for phenotypes until you were tired of that, and then you would begin to make smaller lesions in the coating [sic, coding] sequences for that protein and ask which of the phenotypes was effected by each of the small deletions; and, again, depending on the properties of the protein in the system, you might find that some of the phenotypes were impacted by some of the deletions, and others were impacted by others of these smaller deletions, I should say.

Q: Is there a way before the genetic analysis is done to predict which functions can be separated by selective ablation, and which cannot be separated?

A: In general, I think not. There are probably cases where you can make arguments based on sequence or structure, but, in general, I think not.

126. According to Dr. Curiel,

> ...unpredictability in deriving a vector could originate at whether or not you could derive a practicable cell line that made the transcomplementing function, whether that function was made at the right time in the right amount and whether or not the provision of that function in trans allowed realization of useful amounts of virion. [Ex 1040, p. 47, l. 20 - p. 48, l. 6.]

127. As indicated by both Dr. Kovesdi (Ex 2009, ¶ 9) and the Kovesdi '416 specification (Ex 1001, p. 8, l. 21 - p. 10, l. 6), cell lines that complement single mutations in E1, E2A and E4 had been available prior to the filing of Kovesdi '416.

128. However, according to Dr. Curiel, "[t]he successful production of a [sic] one complementing cell line, even for a single gene region, does not suggest that the same cell line will be useful for complementing any other deficient adenoviral gene region" (Ex 2012, ¶ 16).

129. For example, A549 cells but not Vero cells can be stably transfected with E1 expression plasmids to produce an E1 complementing cell line (Ex 2020, ¶ bridging pp. 76-77). Vero cells could be transfected to produce an E4 complementing cell line, i.e., the W162 cell line, but not to produce an E1 complementing cell line (id., p. 80, c. 1, ¶ 2). Ad2 synthesis of late proteins is blocked in monkey cells (Ex 1052, p. 1243, c. 1, ¶ 1).

130. According to Dr. Kovesdi,

> [t]here are numerous reasons for the difficulty in obtaining complementing cell lines that enable the propagation of adenoviruses with deficiencies in one or more essential gene functions in each of two or more adenoviral regions of the adenoviral genome. First, there are technical difficulties associated with the construction of cell lines (see, e.g., Weinberg et al. [Ex 2019], supra at 5383, which states "many segments of DNA do not transform cells, and there is no direct selection for cells that contain

> such DNA and that might support the growth of mutants in those regions of a viral genome"). Second, since a protein can have distinct functional domains, the mere expression of a complementing adenovirus gene within a cell does not assure complete complementation of a deficient gene (see e.g., Brough et al. [Ex 2008], supra at 625, which describes how gmDBP cell lines complement nonviable DBP mutant viruses for growth, but do not allow for plaque formation). Third, there are a large number of structural and regulatory genes that are temporally regulated within the adenovirus genome. Deleting or disrupting one of these genes, and/or providing the missing gene product in *trans* in an inappropriate temporal pattern, level of production, or form, can cripple virus replication by resulting in either minimal or an absence of functional complementation (see, e.g., Fallaux et al., supra at 221, and page 1584 of Krougliak et al., Human Gene Therapy, 6, 1575-1586 (1995), which each discuss how deregulation of gene expression can have deleterious consequences in terms of virus propagation). Fourth, some adenovirus gene products function at stoichiometric levels in adenovirus replication that are toxic to the recipient cell (e.g., E2A-DBP (Klessig et al. [Ex 1008], supra) and potentially pIX (Krougliak et al., supra)). Such toxicity can confer upon cells having reduced expression of the gene a growth advantage as compared to a cell containing the deficient gene (Krougliak et al., supra at 1584), resulting in an inability to obtain cell lines that contain the complementing gene and, hence, an inability to propagate adenoviruses deficient for that gene. [Ex 2009, ¶ 10.]

131. Dr. Ketner agreed that complementation of late genes would have been difficult in 1994 because complementation with cell lines presents a toxicity problem. However, cytotoxicity is a much less difficult problem if complementing helper viruses are used for complementation. [Ex 1044, p. 51, ll. 3-21; p. 52, ll. 2-7.]

F. Amount of direction or guidance presented

132. Dr. Curiel testified that

> [t]he '416 application does not describe or even suggest an approach for creating, for example, vectors with deficiencies in E2B, MLP-L1, the 13.5 kD gene, late genes (e.g., L1-L5), pIX, the ITRs or packaging sequences, or how to create cell lines capable of complementing deficiencies of all

> early and late gene regions sufficiently to produce the vectors as claimed" (Ex 2012, ¶ 15).
>
> * * * * * *
>
> The '416 application does not provide any guidance for selecting cell lines that would be useful in producing a complementing cell line as described in Claims 89 and 92-94. ... The successful production of a [sic] one complementing cell line, even for a single gene region, does not suggest that the same cell line will be useful for complementing any other deficient adenoviral gene region. [Id., ¶ 16.]
>
> * * * * * *
>
> The '416 application ... does not describe or provide any guidance for how to construct complementing cell lines using adenovirus sequences other than Ad2 and Ad5, even for 293 or A549 cell lines (id., ¶ 19).

133. Dr. Curiel further testified that the '416 application provides "extremely limited instruction on selecting a promoter to express complementing adenoviral genes in a cell line" in view of the admitted "complexity associated with expressing any given Ad gene at the appropriate time, in sufficient quantities, but without being toxic to the cell" (Ex 2012, ¶ 28).

134. Kovesdi '416 reads:

> ...In order to avoid cellular toxicity, which often accompanies high levels of expression of the viral products, and to regulate the temporal expression of the products, inducible promoter systems are used. For example, the sheep metallothionine inducible promoter system can be used to express the complete E4 region, the open reading frame 6 of the E4 region, and the E2A region. Other examples of suitable inducible promoter systems include, but are not limited to, the bacterial lac operon, the tetracycline operon, the T7 polymerase system, and combinations and chimeric constructs of eukaryotic and prokaryotic transcription factors, repressors and other components. Where the viral product to be expressed is highly toxic, it is desirable to use a bipartite inducible system, wherein the inducer is carried within the viral vector and the inducible product is carried within the chromatin of the complementing cell line. Repressible/inducible expression systems, such as the tetracycline expression systems and lac expression system may also be used. [Ex 1001, p. 14, l. 34 - p. 15, l. 17.]

G. Presence or absence of working examples

135. There are eleven (11) examples presented in Kovesdi '416 (Ex 1001, pp. 20-33).

136. Examples 1 and 2, depicted in Figures 1 and 2, disclose construction of vectors deficient in one essential, ΔE1, and in one non-essential, ΔE3, gene region. Since E4 ORF6 provides the essential gene function of E4, the vector of Example 2 remains a "singly-deficient" vector. Examples 1 and 2 are the only examples which indicate that the disclosed vector was successfully produced using HEK 293 complementing cells as evidenced by plaque formation on cell monolayers. [Ex 1001, pp. 20-24; Ex 2012, ¶¶ 12 and 22.]

137. Example 3 discloses construction of a complete ΔE4 vector and states that "all manipulations for viral construction are carried out in the new 293/E4 cell line or 293/ORF6 cell line (described in Examples 8 and 9, respectively)" (Ex 1001, pp. 24-25). Example 4 discloses construction of a ΔE1ΔE2AΔE4 cell line and states "the recipient cell line for this virus construction is the triple complementing cell line 293/E4/E2A" (id., pp. 25-26).

138. Example 5 discloses construction of a ΔE3 vector, while Example 6 further deletes gene region E4 from the vector of Example 5 and Example 7 reinserts E4 ORF 6 into the vector of Example 2 (Ex 1001, pp. 26-28).

139. Examples 8 through 11 describe construction of complementing cell lines. Example 8 adds E4 gene function to the genome of a 293 cell line, while Example 10 further adds E2A gene function to the cell line of Example 8. Example 9 adds E4 ORF6 gene function to the genome of a 293 cell line. Example 11 describes using an A549

parental cell line in place of the 293 cell line for constructing similar complementing cell lines. [Ex 1001, pp. 28-33.]

140. Dr. Kenter conceded that complementation of late genes is difficult, that it is not taught in Kovesdi '416 and that the skilled artisan would have to experiment to know if complementing for all late gene functions was possible using cell lines (Ex 2042, p. 28, l. 16 - p. 29, l. 4).

141. There is no working example of using a repressible promoter to control expression of transcomplementing DNA sequences in a complementing cell line in Kovesdi '416.

H. Quantity of experimentation necessary

142. The Examiner required evidence of enablement for Kovesdi '416 vector and complementing cell lines "in view of the high degree of difficulty and unpredictability in the field of the invention" (Ex 2014, p. 5, ¶ 2).

143. A supplemental declaration by Dr. Kovesdi (Ex 2018) described complementing (i) ΔE1ΔE4, (ii) ΔE21A and (iii)(a) ΔE1ΔE4 and (b) ΔE2A vectors in (i) 293/ORF6 (ii) 293/E2A and (iii) 293/E2A/ORF6 cell lines.

First, this limited showing is not commensurate in scope with the claimed invention. Second, Dr. Kovesdi's results taken in combination with the data (Exs 1032-1034) submitted in connection with Kovesdi preliminary motion 2 supra are confusing and sometimes contradictory. Third, while Dr. Kovesdi indicates that the described vectors and cell lines were made essentially according to the methods described in the Kovesdi '416 application, he did not explain what the differences were and how they

might have affected the results obtained.

I. Analysis

While the level of skill in the art is high, at least the breadth of the claims (which is not limited to vectors reciting combinations of deletion of essential gene functions of ΔE1ΔE4, ΔE1ΔE2 or ΔE2AΔE4, complementing cell lines therefor and methods of using complementing cell lines) and the limited amount of guidance and working examples weigh in favor of nonenablement.

Undoubtedly, it is well within ordinary skill in the art to delete genetic material per se from any genome, e.g., using conventional restriction enzymes. However, given that the deleted genetic material must comprise one or more essential adenoviral gene functions and given the complexity of the adenoviral genome and life cycle, the skilled artisan must know not only what genetic material to delete, but also how to resupply the vector with the missing genetic information in the appropriate amount at the appropriate times in order to allow the vector to propagate.

Assuming without deciding that the overall organization of the adenoviral genome is conserved among serotypes such that specific functions are similarly positioned, the claims at issue are not limited to any particular serotype or even subgroup or subgenera. While members of human adenovirus subgroup C may have highly homologous DNA, the same is not true for other human adenovirus subgroups. Moreover, the claims at issue are not limited to human adenoviruses.

Little guidance is given in Kovesdi '416 with regard to vectors with deletions in other than the E1, E2A and E4 regions. Additionally, some genes direct more than a

single gene function and Dr. Ketner has testified that Kovesdi '416 lacks sufficient disclosure to enable the skilled artisan to delete a single gene function, without deleting the remaining functions directed by that gene. For example, Kovesdi '416 does not exemplify how to construct adenoviral vectors deficient in E2B, MLP, late genes L1-L5, protein IX (which overlaps with the E1B region), ITRs and packaging sequences. Dr. Ketner suggested that individual genetic analysis would need to be done before one could identify which gene functions could or could not be separated by selective ablation.

In short, the prior art and Kovesdi '416 do not provide sufficient information of the location of replication-essential regions of the adenoviral genome commensurate in scope with the serotypes, subgroups, subgenera and genera of the adenovirus family to enable the skilled artisan to create replication-defective vectors and complementing cell lines therefor commensurate in scope with the breadth of Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 without undue experimentation.

Assuming arguendo that one knew how to selectively ablate a desired essential gene function, the complementation problem remains. Use of complementing cell lines for singly-deficient adenoviral vectors was known, e.g., 293 cells supplied E1 gene function and W162 cells supplied E4 gene function. However, Dr. Curiel testified that there was no expectation of success of a unique vector or cell line based on the reported success of another. Moreover, claims 89 and 92-94 are unrestricted as to parental cell line. Further, there is no disclosure in Kovesdi '416 of integrating nonhuman nucleic acid sequences into a human parental cell line, e.g., 293 or A549, to

produce a complementing cell line for a nonhuman adenoviral vector. Dr. Kovesdi himself testified to the large number of structural and regulatory genes that are temporally regulated within the adenoviral genome. Inappropriate temporal expression, level of production or form can result in either minimal or no functional complementation in *trans* by complementing cell lines. Dr. Ketner conceded that complementing certain essential gene functions, e.g., E2B, MLP, L1, and VA-RNA, is unpredictable in the context of a complementing cell line. In other words, successful creation of one complementing cell line is not predictive of any other cell line or even of the same cell line complementing for different replication-essential deficiencies in the same adenoviral vector.

Finally, the use of helper viruses prior to 1994 to complement for deficiencies in the adenoviral genome does not per se enable the Kovesdi claims at issue. According to the prior art, a replication-defective adenoviral vector grown in the presence of a replication-competent adenoviral helper virus tends to disappear from the viral stock. Kovesdi '416 contains no examples of using a helper virus to make and use a replication-defective adenoviral vector. Kovesdi '416 is silent as to what levels of helper virus contamination were acceptable and attainable to allow use of vector stocks contaminated with helper virus.

In short, the framework provided by the Kovesdi '416 application is insufficient to enable the skilled artisan to make and use the full scope of Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95.

J. Wang's contingent request for a judgment of no interference-in-fact as to Kovesdi claim 19 is procedurally improper and evidentiarily unsupported.

Contingent upon grant of Wang preliminary motion 2, Wang requests a judgment of no interference-in-fact between Wang's claims and Kovesdi claim 19 (Paper 44, p. 24). As pointed out by Kovesdi in its opposition (Paper 53, p. 25), this "contingent" request is both procedurally improper and not supported by evidence showing that Wang is entitled to the relief requested. Therefore, this "contingent" request is denied with prejudice.

For the above reasons, Wang preliminary motion 2 is **granted**, Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 are not supported by a fully enabling disclosure.

VIII. Wang miscellaneous motion 1

Pursuant to 37 CFR §§ 1.635 and 1.642[30] (See Paper 33), Wang moves to add U.S. Patent 5,994,106 to the interference and to designate claims 1-19 thereof as corresponding to Count 1 (Paper 42). Kovesdi opposes (Paper 51); Wang replies (Paper 62).

Before claims can be designated as corresponding to a count, there must be an interference-in-fact. In other words, only claims of an involved patent or an involved application can be designated as corresponding. As noted by Wang, "the question of interference-in-fact is a two-way test" (Paper 42, p. 5). Here, we do not see how and Wang has not pointed out how the subject matter of any count in this interference is

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[30] 37 CFR § 1.642 reads: During the pendency of an interference, if the administrative patent judge becomes aware of an application or a patent not involved in the interference which claims the same patentable invention as a count in the interference, the administrative patent judge may add the application or the patent to the interference on such terms as may be fair to all parties.

anticipated or rendered obvious by any claim of Kovesdi patent '106 and vice versa. In particular, we do not see how the replication-defective adenoviral vector and complementing cell lines subject matter of any count anticipates or renders obvious a stock of replication-competent adenovirus free adenoviral vectors and vice versa. In other words, it is not apparent to us that Kovesdi patent '106 claims the same patentable invention as a count in the interference and Wang has not shown otherwise.

Moreover, the issue in seeking to designate a claim as corresponding to a count is to establish that if the opponent wins on the issue of priority, the subject matter of the claims sought to be designated as corresponding to the count would be unpatentable under 35 U.S.C. § 102(g)/103 over the subject matter of the claims of the winning party. Thus, at least one claim of U.S. Patent 5,994,106 ("Kovesdi patent '106", Ex 2032) must define the same patentable invention as at least one claim of the involved Wang '680 application. This Wang has not done.

Therefore, Wang miscellaneous motion 1 is **denied**.

IX. Kovesdi miscellaneous motion 1

Kovesdi moves to suppress Wang Exhibit 2043, the sworn testimony of Monika Lusky-Helm, Ph.D., in Interference 104,821 (Paper 71). Wang opposes (Paper 76); Kovesdi replies (Paper 79).

Kovesdi miscellaneous motion 1 is moot insofar as we have not relied on the testimony of Dr. Lusky-Helm (Ex 2043) in this interference.

X. Order

Therefore, upon consideration of the record, and for the reasons given, it is:

ORDERED that Kovesdi preliminary motion 2 under 37 CFR § 1.633(c)(4) for judgment that Kovesdi claims 39, 45, 48, 51 and 94 do not correspond to any of Counts 1-6 is **denied**.

ORDERED that Kovesdi preliminary motion 3 under 37 CFR § 1.633(c)(2) to amend Kovesdi claim 19 is **dismissed** as moot.

ORDERED that Kovesdi preliminary motion 1 under 37 CFR § 1.633(a) that Wang claims 52 and 54 are based on a specification which, as filed, does not satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, is **granted**. Wang claims 52 and 54 are unpatentable under 35 U.S.C. § 112, first paragraph.

ORDERED that Wang preliminary motion 4 under 37 CFR § 1.633(a) that Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 are indefinite in reciting the term "essential gene function" is **denied**.

ORDERED that Wang preliminary motion 3 under 37 CFR § 1.633(a) that Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 lack written description support for the term "essential gene function" is **denied**.

ORDERED that Wang preliminary motion 2 under 37 CFR § 1.633(a) that Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 are not enabled throughout their scope is **granted**. Kovesdi claims 20-21, 24-26, 36-87, 89-90 and 92-95 are unpatentable under 35 U.S.C. § 112, first paragraph (lack of enablement).

FURTHER ORDERED that in view of the granting of Wang preliminary motion 2, Wang's "contingent" request for judgment of no interference-in-fact between Wang's involved claims and Kovesdi claim 19 is **denied** with prejudice.

ORDERED that Wang miscellaneous motion 1 under 37 CFR §§ 1.635 and 1.642 to designate claims 1-19 of U.S. Patent 5,994,106 as corresponding to Count 1 is **denied**.

ORDERED that Kovesdi miscellaneous motion 1 under 37 CFR § 1.635 to suppress Wang Exhibit 2043 is **dismissed** as moot.

RICHARD TORCZON
Administrative Patent Judge

CAROL A. SPIEGEL
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

Enc: MEDICAL VIROLOGY, fourth edition, White and Fenner (eds.), Academic Press, San Diego (1994), pp. 306-309.

MICROBIOLOGY: An Introduction, by Tortora et al., The Benjamin/Cummings Publishing Company, Inc., Menlo Park, California (1982), pp.321-22

Standing Order (Revised May 2003)

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INTERFERENCE DIGEST

Interference No. 105,136 Paper No. 46

Name: Quig Wang et al.

Serial No.: 08/333,680 Patent No.

Title: Novel Adenoviral vectors, packaging cell lines, recombinant adenoviruses and methods

Filed: 11/03/94

Interference with Imler et al.

DECISION ON MOTIONS

Administrative Patent Judge,_____ Dated,_____

FINAL DECISION

Board of Patent Appeals and Interferences, Adverse Dated, 5/18/04

Court,_____ Dated,_____

REMARKS

Redeclaration Ltr 9/4/03 #47

This should be placed in each application or patent involved in interference in addition to the interference letters.